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The Journal of Allergy

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Original Articles

ARTIFICIAL SENSITIZATION OF INFANTS TO POISON IVY*†

HENRY W. STRAUS, M.D.
BROOKLYN, N. Y.

IN A STUDY of dermatitis venenata published in 1922, Spain[1] showed, by means of the patch test, that approximately 65 per cent of patients over eight years of age are sensitive to the active principle of poison ivy, *Rhus toxicodendron radicans* (L). He employed both an alcoholic and a chloroform extract in testing. With the same technic as employed in adults, he also tested 18 infants between the ages of five weeks and eighteen months. No positive reactions occurred. He then concluded that, with the technic employed, infants could not be shown to be susceptible.

Coca[2] applied the test to a small series of 12 children, five years of age or younger, and he also found that a considerable difference of susceptibility to poison ivy existed between adults and children under five. Of his 12 cases, 2 were under one year; the others ranged between three and five years. Only 1 of these was found susceptible, a boy of five years.

Because of the high percentage incidence of dermatitis venenata in the white race, Coca and Cooke[3] included this form of hypersensitiveness in their classification under the subdivision of normal forms together with serum disease. Under abnormal forms were placed (1) anaphylaxis, (2) hypersensitiveness of infection, (3) atopy. Cooke quoted the figures of Spain (64 per cent positive of 104 cases including children and adults) and said that this percentage may be considerably increased by the use of stronger extracts; but that no reaction was obtained with the strongest extract in children under three. He concluded that dermatitis venenata is a form of hypersensi-

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†Read before The Society for the Study of Asthma and Allied Conditions, New York City, December 6, 1930.

tiveness because the reaction is mediated by a special mechanism that is absent in animals and is not developed in human beings until the age of three.

Brown[4] concluded from his experiments that there is a variability in susceptibility in different persons, and in a given person at different times, but that there is no evidence that would suggest that an absolute insusceptibility to poison ivy exists. On the other hand, Heinbecker[5] found that the Baffin Island Esquimo is not susceptible to the active principle of *Rhus toxicodendron radicans* (L). He tested 65 patients, ranging from infancy to old age, by painting the concentrated extract on an area of skin and allowing it to dry on. Observations were made over a period up to one week. The results were invariably negative. He considered this lack of susceptibility to be due to a lack of contact (poison ivy does not grow in the Baffin Islands) rather than to a lack of any racial characteristics essential to the development of susceptibility. That race can at best cause only a slight quantitative difference in susceptibility is shown by the work of Deibert, Menger, and Wigglesworth,[6] who studied the relative susceptibility of the American Indian as compared to the white race, using the patch method. Their results were: Indians, 56 per cent positive; whites, 58.8 per cent positive. It is evident that in order for sensitivity to develop, there must be sufficient previous contact.

Using *Primula obconica*, Low[7] experimented on himself and others (adults) to see whether individuals could be artificially sensitized. Before beginning to experiment on himself, he could handle *Primula* and rub the leaf on his skin with impunity. He scraped the skin of the left forearm with a scalpel over a small area of about one inch by one-half inch until a moist oozing was produced. In this area, the crushed leaf of *Primula obconica* was vigorously rubbed and the juice allowed to dry on. About twelve hours later, the part was thoroughly washed with soap and water. The area crusted over and healed thoroughly in about two weeks. At no time was there any itching or inflammatory reaction beyond what is normal in a traumatic lesion. Three weeks after this inoculation, the unbroken skin of the same area on the left arm was again rubbed with the crushed leaf of the same *Primula* and the juice allowed to dry on. About eight hours later, there was intense itching and the rubbed area showed redness and slight swelling. Twelve hours later, there was more redness, edema, and itching and in the center of the reaction, there were numerous minute vesicles. It required twenty-eight days for the skin to return completely to normal. Later, the test was applied to the other arm and to the thigh with the same results. Low repeated the experiment on 8 persons and was able to sensitize 2 and failed in 6. He stated that sensitization once produced seems to last for a very long time, probably for life. One attack of dermatitis venenata does not

make the person less sensitive. On the contrary, he seems to become more so, especially if the attacks follow each other closely.

Nestler (quoted by Low[7]), in 1904, rubbed his own unbroken skin with parts of the plant (*Primula*) repeatedly at unstated intervals. He also fixed a part of the plant onto the skin with sticking plaster for some hours at a time. After fourteen days of experimenting, he had a marked reaction to the juice of the plant. Low found also that while his whole skin was sensitized, he could rub the *Primula* leaf on the mucous membrane of his mouth and nose without producing any reaction.

Bloch,[8] some time later working with a concentrated extract of *Primula*, painted the skin of normal persons on an area of four square centimeters after abrasion with sandpaper. After the first, also frequently after the second and third painting, a vesicular inflammation appeared at the site of application.

The work of these authors with *Primula* suggested the possibility of artificially sensitizing persons to poison ivy. As previously stated, it had been shown that no positive reactions had been obtained with the strongest extracts of poison ivy in children under the age of three. Here, then, was a logical field for the experiment of artificial sensitization. At the Cumberland Hospital* abundant clinical material was available in the nursery; and, knowing from the experience of others that the extract of poison ivy could of itself produce no harmful effects, it was decided to make use of these infants.

PREPARATION OF MATERIALS

The materials used in this work were obtained from Dr. A. F. Coca of the New York Hospital and were prepared by him in the following manner:

The fresh leaves of the plant (*Rhus toxicodendron radicans* [L]) were placed in a large funnel and toluol was poured over them. The toluol extract from the first portion of leaves was used for extracting successive portions of leaves in order to keep down the volume of the extract. The extract was placed before a clean electric fan and in this way, a soft waxy residue was left adherent to the wall of the vessel. The last vestige of moisture was driven off by warming the vessel slightly over a Bunsen burner, followed by further fanning. The solid extract was scraped off the vessel and preserved in a tightly stoppered glass tube. This residue was completely soluble in toluol but only partially so in absolute alcohol. The alcoholic extract used was a 5 per cent extract of this material in absolute alcohol. For the skin applications (patch tests) the solid residue was mixed with an equal weight of lanolin to make a paste.

*Service of Drs. Thurman B. Givan and John A. Monfort.

THE POTENCY OF MATERIAL

The potency of the ivy paste was determined by applying it as a patch test to forty-one atopic and normal adults after the method described by Spain and originally used by Cooke, viz.: pieces of adhesive plaster, one inch square, were cut and in the center of the adhesive surface of each, a piece of glazed paper one-quarter inch square was placed. A very small amount of the ivy paste was then applied to the flexor surface of the forearm with the end of a wooden applicator. The patch was applied so that the glazed paper came in direct contact with the paste, thus preventing its absorption by the adhesive material. The patches were left in place for a period of from three to five days and the sites washed off with benzene. Results were read at the end of one week or longer. Of the 41 adult patients tested, 29 were positive when seen in one week, 1 positive in ten days, and 1 required twenty-two days. Ten patients gave a negative result. Expressed in percentages, the test material gave positive reactions in 75.6 per cent of these 41 adults. The reactions varied in intensity from slight erythema and itching, to erythema with itching, papulation and vesiculation at the site of application, and could be graded from one-plus to four-plus. In 3 patients with very marked reactions, there was abrasion and spreading of the reaction from the original site of application of the material. These lesions healed entirely in from two to three weeks leaving no scar, but only an area of light brownish pigmentation, which gradually faded out after several weeks.

THE INITIAL PATCH TEST

One hundred and nineteen newborn infants, ranging from one to four days of age, were tested by the patch method with the poison ivy paste. In some of these, the test was applied in the orthodox manner to a spot on the back in the region of the scapula. This location is well suited because of easy accessibility. In others, in addition to the usual patch on the unbroken skin, another patch was applied at the same time on the opposite side to an abraded area of skin, produced by lightly stroking an area about one-quarter inch square with a pumice stone. The ivy paste was then lightly rubbed into the abraded area and the patch applied. Also at the same time, these infants (71 in number) were fed an ivy solution made by placing one cubic centimeter of the alcoholic extract on enough sugar of milk to soak it up and then adding water to make a 10 per cent solution, which had a muddy appearance because of the undissolved sugar of milk. Two drops of this solution were fed once a day, being placed on the back of the tongue with a medicine dropper, starting on the day of the test and continuing during the stay in the hospital. The material was not vomited. The average amount ingested by each infant was 14 drops.

The patches were allowed to remain in place until the day of observation, which in most cases was between six and eight days after application. A few were seen earlier and some later. The average number of days of observation for the whole group was seven days. Benzene was used to remove the patches and to wash off the sites. *In no case was there any variation from the normal appearance of the skin in any of the tests, either on the unbroken or on the abraded skin test sites.* The results were entirely negative in conformity with the findings of others.

THE SECOND PATCH TEST

After an interval of from two to four weeks, the infants who had received the initial test, either by simple application to the skin alone, or by application to unbroken and abraded skin plus feeding, were to be brought to the out-patient department for further testing. Of the original 119 patients, 48 were retested. The second patch was applied to the unbroken skin on the back over the scapula region. The same ivy paste that was used in the initial tests was employed in the second tests. An attempt was made to avoid the exact spot which had previously been used and in some cases the opposite side was used for the second test. The mothers were told to allow the patch to remain in place for two to three days and then to remove it and to wash the site thoroughly with soap and water. The infants were seen again one week after application of the patch test and the results observed. *Thirty-five of the 48, or 72.9 per cent showed a definitely positive reaction on the tested site after one week or longer, and 13 were negative.* (Table I.)

A reaction was considered positive when there existed at the site of application of the material, erythema with papulation, or erythema, papulation, and vesiculation. The appearance was typical of the lesion of poison ivy but of a milder degree, and localized strictly to the site of application of the material. When present, the positive test stood out in sharp contrast to the surrounding normal skin. The erythema was usually a bright red, the affected area being slightly raised with tiny papules or papules and tiny vesicles on the erythematous background. The reaction did not fade into the surrounding normal skin, but was sharply outlined after the pattern of the glazed paper on the patch. Variations in intensity of reaction were noted, so that it was possible to grade them from one-plus to three-plus. In general, they were milder than the reactions observed in the adult group, and none were seen which could be called four-plus. None of the reactions in the infants showed any tendency to spread from the site of application of the material; nor was abrasion, such as was observed in the markedly positive cases in adults, ever seen in the infants.

TABLE I

SHOWING THE RESULTS OF THE PATCH TEST AFTER THE INITIAL APPLICATION OF THE MATERIAL

CASE NO.	NAME	SEX	RESULT 1ST TEST	DAYS SINCE OBSERVATION 1ST TEST	DATE 2ND TEST APPLIED	DATE OBSERVED	RESULT 2ND TEST	DESCRIPTION OF REACTION
7	G	M	0	27	8/15/30	8/22/30	+	E. and P.
9	C	M	0	45	8/15/30	8/22/30	++	E. and P.
15	S	M	0	27	8/15/30	8/22/30	+	E. and P.
17	T	M	0	20	8/15/30	8/22/30	++	E. and P.
18	S	F	0	27	8/15/30	8/22/30	++	E. and P.
21	H	F	0	20	8/ 1/30	8/ 8/30	+++	E., P., and V.
26	M	F	0	16	8/ 1/30	8/ 8/30	0	
						8/15/30	0	
27	E	M	0	16	8/ 1/30	8/ 8/30	+	E. and P.
29*	B	M	0	13	8/ 1/30	8/ 8/30	0	
						8/22/30	0	
30	B	F	0	16	8/ 1/30	8/ 8/30	0	
34	S	M	0	15	8/ 1/30	8/22/30	0	
35	B	M	0	15	8/ 1/30	8/22/30	+	E. and P.
36	M	F	0	13	8/ 1/30	8/22/30	+	E. and P.
38	L	M	0	13	8/ 1/30	8/ 8/30	+	E. and P.
40	S	F	0	6	8/ 1/30	8/ 8/30	0	
						8/15/30	0	
42	S	M	0	11	8/ 1/30	8/ 8/30	+	E. and P.
43	B	F	0	11	8/ 1/30	8/ 8/30	0	
44	M	M	0	9	8/ 1/30	8/ 8/30	0	
45	H	M	0	9	8/ 1/30	8/22/30	+	E. and P.
46	H	M	0	16	8/ 8/30	8/22/30	+	E. and P.
49*	J	M	0	14	8/ 8/30	8/22/30	0	
51*	T	M	0	5	8/ 1/30	8/ 8/30	0	
55	C	M	0	11	8/ 8/30	8/22/30	0	
59	C	F	0	11	8/ 8/30	8/15/30	+	E. and P.
60	G	M	0	67	10/ 3/30	10/10/30	0	
61	F	F	0	10	8/ 8/30	8/22/30	0	
66	D (twin)	M	0	7	8/ 8/30	8/15/30	+	E. and P.
67	D (twin)	M	0	7	8/ 8/30	8/15/30	+	E. and P.
70	D	F	0	12	8/15/30	8/22/30	+	E. and P.
71	B	F	0	11	8/15/30	8/22/30	+	E. and P.
74*	V	F	0	10	8/15/30	8/22/30	0	
75	M	M	0	6	8/15/30	8/22/30	+	E. and P.
80*	B	M	0	14	8/22/30	8/29/30	0	
81	H	M	0	7	8/15/30	8/22/30	+	E. and P.
82	S	F	0	7	8/15/30	8/22/30	+++	E., P., V., and D.
87	T	M	0	36	9/19/30	10/ 3/30	0	
89*	B	M	0	9	8/22/30	8/29/30	0	
90	K	F	0	16	8/15/30	8/29/30	++	E., P., and V.
95	W	M	0	14	8/15/30	8/29/30	++	E., P., V., and D.
98	C	F	0	30	9/19/30	10/ 3/30	+	E., P., and D.
99	B	F	0	21	9/19/30	9/26/30	++	E., P., and V.
100	B	M	0	21	9/19/30	9/26/30	0	
						10/ 3/30	+	E. and P.
101	E	F	0	31	9/19/30	9/26/30	+	E. and P.
103	P	M	0	31	9/19/30	9/26/30	+	E. and P.
107	D	F	0	21	9/19/30	9/26/30	++	E. and P.
110	H	F	0	25	9/19/30	9/26/30	+++	E., P., and V.
114	M	F	0	22	9/19/30	9/26/30	++	E. and P.
115	P	M	0	20	9/19/30	9/26/30	++	E. and P.

*Cases 29, 49, 51, 74, 80, and 89 among the negative reactors were given a third patch test after a suitable interval. Cases 49, 51, and 74 then gave positive reactions, while Cases 29, 80, and 89 remained negative.

Explanation of Symbols:
Under "description of reactions," E = Erythema, P = Papulation, V = Vesiculation, D = Desquamation.

The reactions subsided very gradually, requiring from two to four weeks for the sites to return completely to normal. In following these patients from week to week, it was possible to observe first the disappearance of the vesicles and papules, then the fading of the erythema and its replacement by a light brownish pigmentation and finally in some of the cases, desquamation of the site occupied by the reaction. It was possible in some of the patients who did not report for two or three weeks after the test, to say definitely that a positive reaction had taken place (or was in fact still present), because of this residual evidence. The skin sensitivity seemed to be generalized, for a positive reaction could be obtained on skin sites on the side opposite that to which the initial contact had been applied.

Cases 29, 49, 51, 74, 80, and 89, which on second test proved negative as shown in Table I, were retested with the same ivy paste after a suitable interval. Following this third application, Cases 49, 51, and 74 gave positive reactions and were therefore included in the group of 35 positive reactors, making the total 72.9 per cent. Cases 29, 80, and 89 still remained negative one week after the test. It is reasonable to suppose that still more contact or the use of a stronger extract might cause some of the remaining negative cases to become positive and further increase the percentage of positive reactors. No disturbances of any kind were encountered in any of the infants which could be attributed to either the cutaneous application or the ingestion of the materials.

From the results obtained thus far, it was evident that after the second (in 3 cases the third) application of the ivy paste, a characteristic cutaneous reaction, localized at the test site, was produced in 72.9 per cent of 48 cases, whereas no reaction whatever resulted after the initial application of the same substance in any of them. Some of these patients had been given cutaneous application on unbroken skin; others had had cutaneous application on unbroken skin and on abraded skin, plus ingestion of the ivy solution. In both groups, positive reactions had been obtained with the second patch test. Studies are now being made on sensitization by various routes. These will be reported at a future date.

SUMMARY

A poison ivy paste prepared by Dr. Coca of the New York Hospital was applied as a patch test to 41 normal and atopic adults and gave a positive test in 75.6 per cent of the cases. The same material was applied to the skin of 119 newborn infants with completely negative results. Some of these infants, in addition to skin application, had been fed a solution of poison ivy by mouth. After a suitable interval, 48 of the infants were retested by the patch method and a positive reaction was obtained in 35 cases, or 72.9 per cent. The skin was generally sensitized.

CONCLUSIONS

1. If the results here obtained are confirmed by others, then it would seem that newborn infants may be artificially sensitized to poison ivy by sufficient skin contact with a potent extract.

2. The skin is generally sensitized.

3. The insusceptibility to poison ivy heretofore observed in children under the age of three years was not due to a lack of mechanism, but was due to a lack of previous contact, or a lack of sufficient contact.

4. If the sensitizing contact is adequate, infants will react with a positive patch test in approximately the same percentage as adults.

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41 Eastern Parkway.

EFFECT OF WEATHER VARIATIONS UPON THE SYMPTOMS OF HAY FEVER PATIENTS*

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NEW YORK, N. Y.

IN 1929 a study was made of the possible effect of the daily fluctuations in humidity and temperature upon the degree of symptoms as noted in a series of 103 ragweed hay fever cases treated prophylactically. It was attempted to correlate the findings of the weather reports and the degree of hay fever as noted daily by these patients. It is well recognized that the severity of symptoms depends largely upon the extent of the exposure of the patient to ragweed pollen. Upon days of high pollen concentration severe symptoms will arise in spite of most energetic and thorough pollen therapy, the protection afforded by specific treatment being relative in all classes of pollen sensitiveness.

Hence the variations in symptoms even in the specifically treated patient are largely due to fluctuations in the pollen content of the air, which in turn is directly affected by the humidity, the temperature and the wind velocity as well as the rainfall.

For purposes of comparison, the findings in 1929 are here repeated, being combined with the pollen count of that year, which was not then available but which has been furnished us, together with that of 1930, by Mr. O. C. Durham. A slight difference occurs in the two charts in that the average daily humidity has been employed in the 1930 chart as being more representative than the morning humidity as used in the 1929 chart.

It will be noticed from both charts that the humidity curve is inversely proportional to the symptom curve and the pollen curve; usually when the humidity curve is down, the symptom curve and pollen curve are up, and vice versa. The rainfall also tends to lower the pollen curve and thus lower the symptom curve, as is evident upon the charts.

The symptom curve is based on the results in patients who had been treated for at least ten weeks before the onset of the season as well as during the season. The degrees of severity were designated as "severe," "moderate," and "slight or no hay fever." The cases having "severe" or "moderate hay fever" were grouped together, as opposed to those having "slight or no hay fever." For example, on August 24, in the 1929 chart, 24 per cent of the patients had "severe"

*From the Department of Medicine, and the Department of Pathology and Bacteriology, New York Post-Graduate Medical School and Hospital.

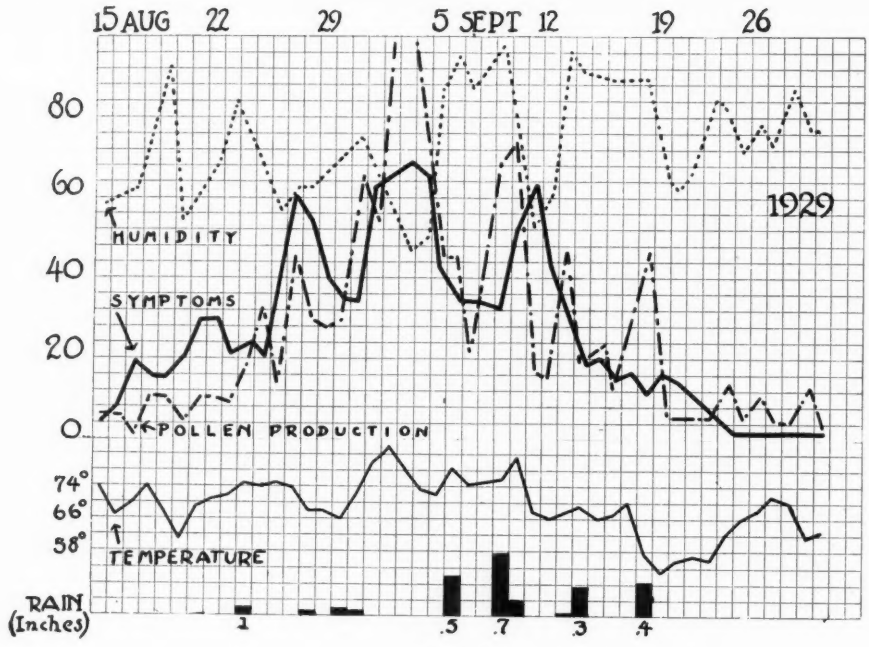

Chart 1.

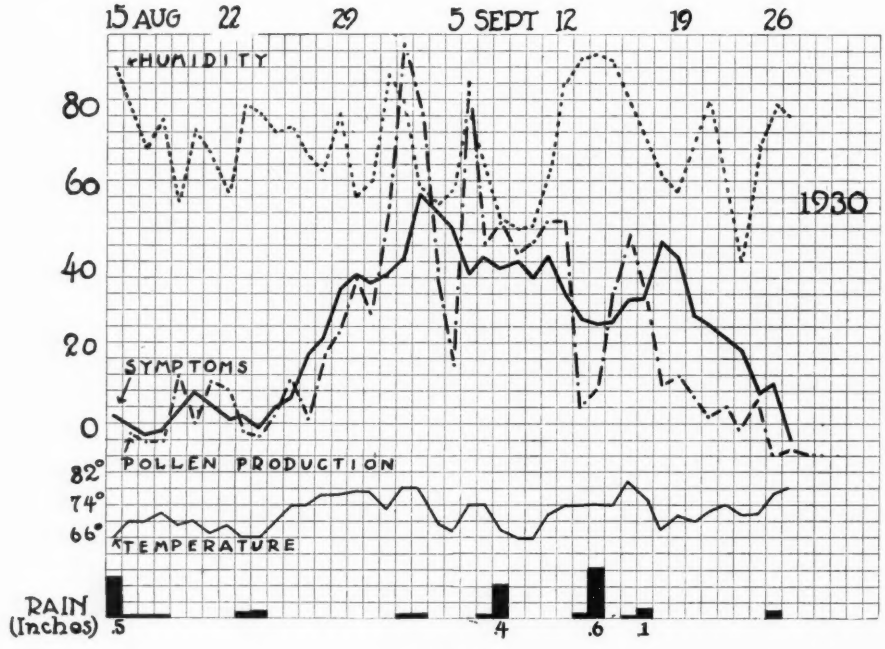

Chart 2.

Charts 1 and 2.—The numbers on the ordinate above the zero mark represent the average humidity, the percentage of patients having "severe" or "moderate" hay fever, and the number of ragweed pollen granules on the slide each day. The numbers below the zero mark on the ordinate represent the average temperature (Fahrenheit). The rainfall in inches is recorded at the bottom of the chart.

or "moderate" hay fever and 76 per cent had "slight" or no hay fever. While it is realized that it is impossible to chart accurately such subjective findings as the patient's report of his symptoms, the average result, as calculated from a group of a hundred cases, should be approximately correct.

It will be noticed on both charts that an increased pollen count frequently precedes by twenty-four hours an elevation in the symptom curve. This can be explained by the fact that the slides upon which are collected the pollen granules for daily calculation are exposed for twenty-four hours from 8 A.M. to 8 A.M., the count of the early morning hours thus being included in the previous day's record.

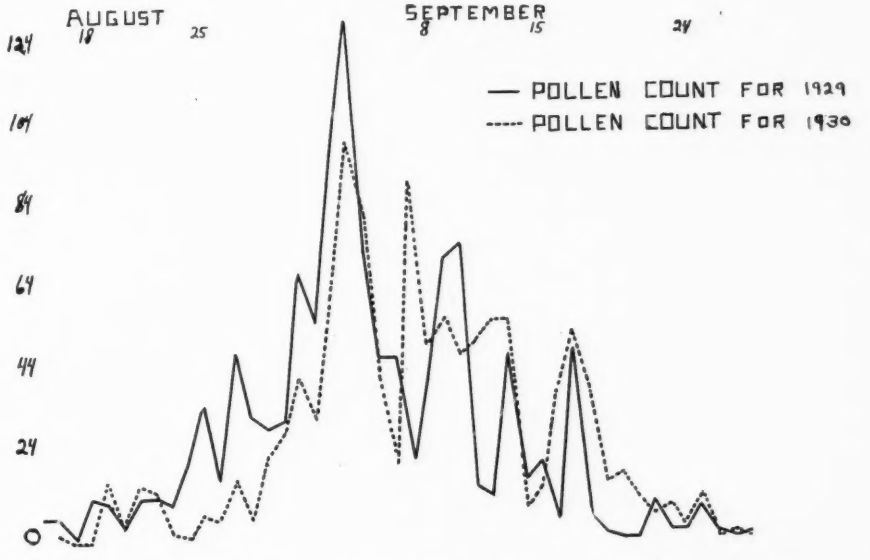

Chart 3.—The pollen counts, which were made by Mr. O. C. Durham, represent so many pollens per cubic yard of air. This was obtained by counting, under low power, five trips across a glass slide with a field width of 1.4 millimeters.

The average temperature for New York City seems to affect the symptom curve also. When the temperature is high, the pollen curve and the symptom curve usually are high. Last year there was more variation in the temperature, the highest being 84° F. and the lowest being 54° F. This year the highest was 80° F. while the lowest was 66° F.

It should be emphasized that the variations in humidity and temperature are considered as affecting the symptoms of the patient not directly but through their influence upon the pollen production. An attempt to chart the daily direction of the wind, and wind velocity in relation to the above-mentioned curve was unsuccessful. It may be said, however, that westerly or southern winds are found usually at times of high pollen concentration, as has been stated by Durham.

It can be seen from these charts that days with high humidity, precipitation and a low temperature, are the days on which there is the least amount of pollen in the air, and consequently a lessening of the symptoms in the patient. Days with a low humidity, no rainfall and a relatively high temperature show an increase in the dissemination of the ragweed pollen.

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DEATH IN ASTHMA*

Report of a Case With Autopsy

A. Murray Fisher, M.D., and James P. Beck, M.D.
New York, N. Y.

SINCE death during an attack of uncomplicated asthma is rare, it seems desirable to report a case which we have had the privilege to observe. The patient clinically was a typical asthmatic, dying in an acute attack and there were revealed on section the characteristic histologic changes described in the disease. An unusual and unexpected feature of the case was a bilateral pneumothorax which did not produce atelectasis and was not considered the cause of death.

CASE REPORT

A. F., a Danish-American gardener, aged thirty-two, was first seen in the out-patient department of the Presbyterian Hospital in July, 1928, complaining of asthma of nine months' duration.

Family history: Negative for asthma,

Past history: The patient was married. His wife was living and well. There were no children. He had had no serious illness and no operations. He had never been subject to coughs, although he had had colds rather frequently. Two years previously, he had an attack of lead colic after painting a greenhouse.

Present illness: He had had a slight cough for one year. Nine months previously he began having attacks of asthma, which became more severe; they were relieved by adrenalin and ephedrin. He had night sweats, lost weight and strength, and his appetite was poor. Physical examination at that time showed a cadaverous man of thirty-two, who was acutely dyspneic. The pupils reacted to light and accommodation. The teeth were in poor condition. The lungs were full of sibilant and sonorous râles. The heart was normal. The abdomen was negative. A diagnosis of asthma was made. Eighteen skin tests were done, using the usual pollens, animal emanations, and foods. None of them showed immediate reactions, but there were late reactions to orris and dust. He was given a mixture containing potassium iodide, belladonna, and compound spirits of ether with some relief. X-rays showed the lung fields to be clear. The urine examination was negative. The patient was followed in the asthma clinic for the next fifteen months, during which time the wheezing asthmatic attacks recurred about once a week, coming on in the morning and lasting

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about one hour after arising. He was given a course of mixed vaccine (Streptococcus hemolyticus, and Streptococcus viridans, Staphylococcus aureus, and Staphylococcus albus, pneumococcus and typhoid bacillus) with injections twice a week; then later a course of typhoid and paratyphoid vaccine. Ephedrin was given for the bad attacks. The asthma and the cough were definitely worse in the fall and winter and in bad weather. In the spring, the attacks became less frequent. An x-ray examination of the sinuses showed marked clouding of the right frontal sinus and some clouding of both antra, but no pus was obtained on irrigation of the antra. The patient was found to be sensitive to hemolytic streptococcus vaccine.

During the summer he continued to improve. In the fall the attacks became severe again, and for six weeks beginning in October, he had an attack of asthma nearly every day. After the attacks he came to the clinic and was treated with ephedrin, with improvement. He was advised to go to Arizona and had packed up to leave when the fatal attack began. During all this time there had been no history suggestive of cardiac insufficiency.

The last attack began three days before admission and the symptoms were more severe than any he had ever had. Ephedrin gave no relief and two doses of adrenalin made him much worse. (On admission he had begged not to be given the drug.) He was given morphine at 11:00 A.M., and entered the ward at 4:00 P.M. on November 27, 1929. He appeared to be gasping his last, sitting far forward, and using all the accessory muscles for inspiration and expiration. Both phases were much prolonged, especially expiration, which was long and wheezing and not completed before another inspiration was attempted. His face was ashy gray; his lips, ears, and hands were cyanotic. The neck veins were engorged. He was sweating profusely. His temperature was 101° p.r., pulse 136, respirations 28, blood pressure 130/80. The pupils were constricted. The throat was not examined. There was no general glandular enlargement. The chest expansion was very poor, and the interspaces and costal margins were pulled in with each inspiration. The lungs were hyperresonant; sibilant and sonorous râles were heard throughout both lungs, more pronounced in expiration. The heart did not seem enlarged to percussion, although the borders were not accurately determined. The sounds were distant, rapid and regular, without murmurs. The abdomen was negative (patient sitting up). There was no edema and no clubbing of the fingers. The patient failed rapidly. He was given: ephedrin, 0.05 gm., subcutaneously, twice; a phlebotomy; morphine (0.015 gm.) at 4:15 and again at 7:20; and 0.3 gm. of digifoline. He became more comfortable temporarily but the bronchial spasm never relaxed. The pulse grew weaker and weaker, the blood pressure fell to 70/0, the respirations became more and more labored and the final gasp came a

few moments after the second dose of morphine, three hours after admission to the ward. Intracardiac adrenalin did not start the respirations again. Death was apparently due to asphyxia. The blood Wassermann was anticomplementary. Unfortunately no blood count was obtained.

AUTOPSY REPORT

The autopsy was performed sixteen hours postmortem. The important findings were the following:

Thoracic Cavity.—The pneumothorax test is positive on both sides. Approximately 300 c.c. of air escapes from the left pleural sac and about 100 c.c. from the right (estimated). The lungs are extremely voluminous and they do not collapse after the sternum and cartilage have been removed. The anterior margin of the right lung extends to the pleural limits beneath the sternum. The left lung partially covers the pericardial sac. The air space between the lung and chest wall, in each pleural sac, is slightly greater in the apical regions. There are no fibrous adhesions. The fourth, fifth, and sixth thoracic vertebrae are involved in a right scoliosis. There is no evidence of caries in these vertebrae.

Heart.—Weighs 300 grams. The apex is formed in part by the right ventricle which is moderately hypertrophied. There is some dilatation in the conus area. The epicardium is smooth and transparent everywhere, but slightly wrinkled over the right ventricle. The endocardium of the right auricle is smooth and shining. The tricuspid valve, the right ventricle, and the pulmonary valve are normal. The myocardium is dark red and firm. The left auricle is normal. The leaflets of the mitral valve are slightly thickened. Upon the opposing surfaces of the leaflets are three or four small, firm, yellowish, beaded nodules about 0.5 mm. in diameter. Many of the chordae tendineae are somewhat thickened at the valvular end. The anterior papillary muscle is a little hypertrophied. The muscle of the left ventricle is firm and dark red. The endocardium over the upper portion of the septum is greyish and slightly thickened. The cusps of the aortic valve are slightly thickened; at the base of each is an atheromatous plaque. The adjacent edges of the anterior and right posterior leaflets are adherent for a distance of 3 mm. The coronary arteries are essentially normal. The aorta is elastic. There are a few small atheromatous plaques in the intima.

Left Lung.—The left lung weighs 440 grams. It appears voluminous and air-containing in all portions. The surface is smooth, shining and pale; the pleura is transparent and dry. The septa are distinct and in places the lobules bulge up between them. Through the pleura the aveoli are visible as tiny round sacs of air of more or less uniform size. On the anterior surface of the anterior margin of the left upper

lobe, there is a round perforation in the pleura which appears like a large pinhole. Opposite it on the medial surface of the same lobe is another similar opening, surrounded by a hemorrhagic zone about 1 to 2 mm. in width. On compression of the surrounding lung, air escapes from this perforation. Both openings appear to result from the same needle-puncture, and were presumably the result of the intracardiac injection of adrenalin and caffeine. Upon section, the surface of the lung is dry and uniformly pinkish-grey. The bronchi and

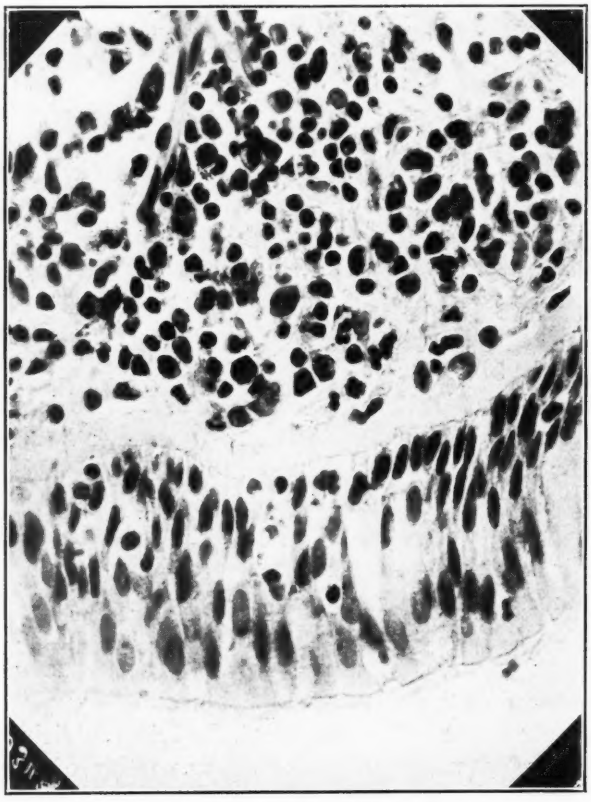

Fig. 1.—Infiltration of trachea.

bronchioles appear to be completely plugged with tenacious mucus. The walls of both larger and smaller bronchi are thickened and the mucous membrane is pale and granular. The vessels around the bronchi are engorged. The lymph nodes are anthracotic and moderately enlarged.

Right Lung.—The right lung weighs 500 grams. Its pleural surface and general appearance are similar to that of the left lung. Upon the anterior surface of the inferior lobe, 6.0 cm. from the inferior margin immediately below the interlobar fissure is a slit-like perforation 3 mm. long having grey, opaque margin surrounded by a zone of hemorrhage

1 to 2 mm. in width. Air escapes from it also. A similar perforation 3 mm. in length is found upon the anterior surface of the upper lobe just above the interlobar fissure. Upon the diaphragmatic surface and on the medial surface of the apex of the lower lobe are several small grey elevated nodules about 1 mm. in diameter having tiny black umbilicated centers. There is hyperemia about those on the basal surface. The cut surface of this lung is similar to the cut surface of the left lung.

Fig. 2.—Cross-section of a bronchus, showing hypertrophy of the muscle, infiltration of the mucosa and submucosa, and plugging of the lumen with mucus in which several Curschmann's spirals are present.

Spleen.—The spleen weighs 60 grams. It is firm and the contours are normal. The color is dark brown. The cut surface is firm and remains level with the capsule. The malpighian corpuscles are numerous but small.

Liver.—The shape and size are normal. It is firm. The lobular pattern is indistinct, and the color is reddish-brown. It appears normal. The gall bladder is normal and contains no stones.

Adrenals.—There is a moderate lipoid deposit. They are normal.

Kidneys.—The left kidney weighs 140 grams and the right, 120 grams.

The left kidney is normal in shape, firm, and reddish-purple in color. The capsule strips easily, leaving a smooth surface. On section the structure of the cortex and the pyramids is normal. The cortex averages 6 mm. in depth. The color is reddish-brown throughout. The glomeruli are seen as dark red dots. The striations of the pyramids are normal. The right kidney resembles the left. Both ureters are normal.

Pelvic Organs.—The bladder, prostate, seminal vesicles, and testes are normal.

Fig. 3.—Infiltration of bronchus.

Alimentary Tract.—Normal except for a Meckel's diverticulum, 6 cm. in length and 5 cm. in circumference, found 1 meter above the ileocecal valve.

Brain and Cord.—Not examined.

MICROSCOPIC FINDINGS

Heart.—Left ventricle: There are small scars around two arterioles, otherwise it is normal.

Mitral Valve.—The valve is thickened by fibrous tissue, throughout which are scattered a number of lymphocytes. Near the base of the

valve at the site of attachment of a thickened chorda tendinea are broad hyaline bands which contain a few nuclei which usually contain an irregular nucleolus. About halfway between the base of the valve and its extremity, the valve is again thickened by hyaline tissue. Upon the surface of this mass the endothelium is missing, and in its place is a mass of homogeneous eosinophilic material. Over this are a few strands of fibrin in whose meshes lie a few pyknotic, distorted nuclei of leucocytes. At the base of this deposit of fibrin are a few large vesicular nuclei having dense rims of chromatin enclosing irregular

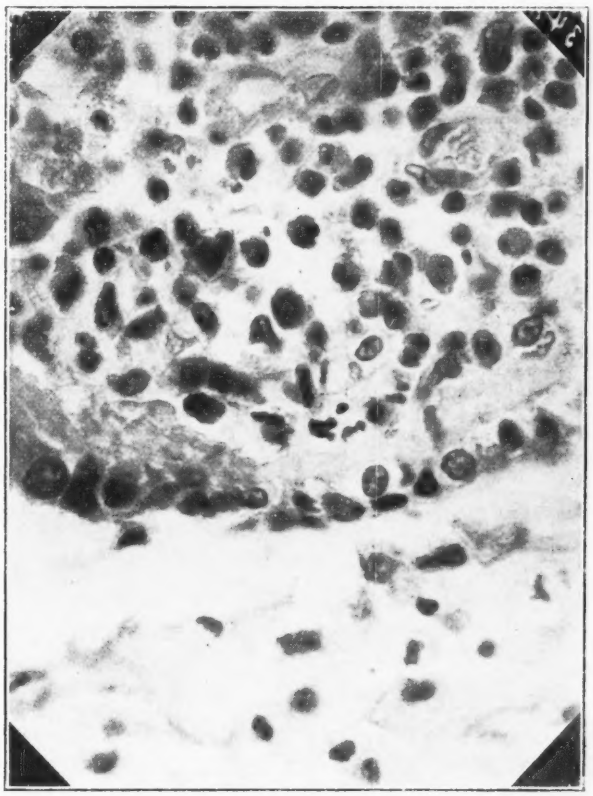

Fig. 4.—Infiltration of bronchus.

coarse clumps of nuclear material. There are many small vessels throughout the valve.

Aorta: Normal.

Trachea.—(Fig. 1.) The mucous membrane is somewhat thickened and the submucosa is edematous. The blood vessels are moderately engorged. Many polymorphonuclear leucocytes and eosinophils lie in the tunica propria and in various levels between the cells of the epithelium. The portion of submucosa nearest the surface is infiltrated with many lymphocytes, plasma cells, and eosinophils. Similar

cells lie among the alveoli of the tracheal glands. These glands show various stages of secretion. Mucus and a few leucocytes are seen in the lumina of the ducts, and upon the surface of the epithelium of the mucous membrane of the trachea.

Right Lung.—A.. The lumina of the larger bronchioles are filled with mucus in which are great numbers of eosinophils, sometimes in clusters; a few polymorphonuclear leucocytes, and clumps of desquamated epithelial cells. Portions of the mucus stain more deeply and appear

Fig. 5.—Lung: contracted bronchiole.

as wavy bands irregularly distributed throughout the mass. (Fig. 2.) The epithelium of the mucous membrane of the bronchioles contains areas of squamous metaplasia. The basement membrane of the epithelium is thickened. Beneath this the submucosa is densely infiltrated with leucocytes consisting of many lymphocytes, plasma cells, and eosinophils and a few polymorphonuclear leucocytes. (Figs. 3 and 4.) The smooth muscle is thickened, containing coarse fibers. The blood vessels are engorged. The bronchial glands resemble the tracheal glands. Many of the cartilage cells are necrotic. The alveoli are markedly distended, with thin septa and engorgement of the capil-

laries. A few septa are broken. There is no exudate or exfoliation of cells into the alveolar spaces. *Gram stains:* No bacteria are seen.

B. The left lung. Changes here are similar to the changes noted above. The section passes through a contracted bronchiole (Fig. 5).

Sections of the other organs show no noteworthy abnormalities. The liver, spleen, and pancreas are normal. The adrenals contain a number of small cortical adenomas. The glands of the prostate contain much infolded columnar epithelium. The testis is normal. The stomach is normal.

The anatomical diagnosis was: Bronchial asthma, pulmonary emphysema, rupture of the lung (right), perforation of lung (left), pneumothorax (bilateral), hypertrophy and dilatation of the right ventricle, chronic rheumatic endocarditis—mitral valve, Meckel's diverticulum, and adenomas of the adrenals.

DISCUSSION AND LITERATURE

The death of this patient resembles that described in acute anaphylactic shock in guinea pigs, which was shown by Auer and Lewis[1] to be due to asphyxia brought on by tetanic contraction of the bronchial muscles. In these animals less and less air leaves the lungs during each expiration until no more air can enter and respirations cease. Their lungs are found "immobilized in an inspiratory state," the bronchioles being probably obstructed by muscular contraction and mucus.

Ellis,[2] in 1908, studied the pathology of asthma as shown by 7 cases collected from the literature and 1 of his own. He tried to arrive at a conclusion as to the cause and mechanism of the asthmatic attack. He found emphysema, mucous plugs in the smaller bronchi, infiltration of the bronchial walls with leucocytes and eosinophils, and spirals of mucus. He did not consider these findings enough to explain all the symptoms in an asthmatic attack, nor do they shed any light on the cause of the disease. He mentioned the theories of the mechanism of the asthmatic attack, the important ones being: "spasm of the bronchial muscles" and "bronchial catarrh." He leaned to the latter view, though the postmortem findings indicate that there is another factor.

Marchand,[3] in 1916, reported two cases of fatal asthma and discussed the origin and significance of the different pathologic findings: the profuse bronchial secretion; the Curschmann's spirals with their central threads; the lymphocytes, mast cells, and eosinophils in the bronchial walls; the Charcot-Leyden crystals; and many crystals of a different kind. In 1918, Marchand[4] added another case, a man of forty-eight years, who worked in a factory, was exposed to poisonous gases, and had had asthma for two years before the final fatal attack. The pathologic findings were: occlusion of many bronchioles with mucus; many

spirals with a dark staining central thread; hypertrophy of the bronchial muscles; eosinophils in the walls of all the air passages, including the nasal mucous membrane; a "local eosinophilia of the whole respiratory tract," suggesting a "systemic disease of the respiratory mucous membrane." There was also moderate hypertrophy of the right ventricle. He discussed the points of similarity and difference between asthma and anaphylactic shock. He also called attention to the fact that in none of his cases was there any active tuberculosis, although asthma and tuberculosis are said to be frequently associated.

Huber and Koessler[5] in reviewing the cases of death in asthma up to 1922 found 15 and added 6 more. In 6 of those collected from the literature and 2 of their own the death can be considered as due entirely to a paroxysm of asthma. From these cases they made a detailed pathologic study and found the most constant findings were: acute emphysema, hyperemia and cellular infiltration of the bronchial walls, especially with eosinophils; increased activity of the mucous glands, and hypertrophy of the bronchial muscle. Thus there is an actual increase in the thickness of the bronchial wall and a constriction of the lumen. They also found ulcerations in some of the bronchi. The muscular hypertrophy and the constriction of the lumina often with infolding of the mucosa constitute good evidence for hyperactivity and spasm of the bronchial muscles as one of the main factors in an asthmatic attack.

Lemierre, Léon-Kindberg, and Lévesque,[6] in 1923, reported a case of a man of fifty-eight years, who had a sudden onset of asthma, recurring attacks, and finally death during an attack with no evidence of an infection. At autopsy, the bronchi were found plugged with a cast-like formation, containing many eosinophiles and Charcot-Leyden crystals.

Rackemann,[7] in 1926, described 5 fatal cases of asthma with the autopsy report on 1 of them. In this one were found many of the changes already described. There was marked emphysema and the walls of some bronchi were infiltrated with inflammatory cells, especially eosinophils. The right ventricle was dilated. The bronchial musculature was not hypertrophied. His cases were women of middle age, whose asthma began after the thirtieth year, who showed little hypersensitivity to foreign substances, and many of whom had foci of infection. He considered the prognosis unfavorable in this type of patient.

Kountz and Alexander,[8] in 1928, studied 3 cases of death in true asthma with autopsies, and report, in addition to the lesions mentioned by Huber and Koessler, rupture of the basement membrane of a bronchiole in 1 case and infiltration and destruction of the bronchial cartilage in another. One of their patients had tuberculosis with cavitation and another had edema, probably not of cardiac origin. They also

found thickening of the walls and narrowing of the lumina in the medium-sized bronchioles (3-7 mm.), with dilatation of the smaller bronchioles behind them.

Cabot's case No. 14,161, in June, 1928,[9] is that of a teamster aged fifty-two years who had had asthma at fourteen, but had been entirely free from it until a year before admission, when there began a series of attacks which finally ended in his death. The pathologic diagnosis was: Asthmatic bronchitis, acute distention of the lungs, and emphysema. There was no cardiac nor renal complication.

Bivings,[10] in 1928, reported a case of a ten-months-old infant with repeated bronchospasms for four days and finally death during an attack. He mentions also a case of Davenport's in Atlanta in a two and a half-year-old child dying of "heart failure in an asthmatic attack."

J. A. Clarke,[11] in 1930, reported a case of a patient fifty-three years old, who had had asthma for twelve years and died during an attack. The author calls attention to the finding of "microscopic atelectasis." He compares this to "macroscopic atelectasis," or massive collapse of the lungs, which he says is more common in asthmatics than in normal people.

C. B. Wright,[12] in 1930, wrote of a sixty-seven-year-old woman, with a history of recurrent bronchitis and asthma, especially in the winter and at night. She died in a paroxysm during which no air could get in or out of the lungs. She was refractory to adrenalin. The autopsy showed obliterative bronchitis. The medium-sized bronchi were almost completely occluded. There was thickening of the mucosa (with infolding), of the submucosa and of the muscle layer, and infiltration with eosinophils. There was no emphysema nor atelectasis.

Harkavy,[13] in 1930, reported 2 cases of asthma with autopsies: the first patient apparently died of cardiac failure, the second in a paroxysm of asthma. The usual pathologic findings were present, including infiltration with eosinophils, though the patients were not "allergic types" clinically. One showed right ventricular hypertrophy associated with marked emphysema of long standing.

Hoover,[14] studying the mechanism of emphysema, found that he could not produce emphysema in dogs by partial obstruction to the expiratory phase unless hyperpnea were induced, so that one expiration could not be finished before another inspiration was necessary. The same mechanism might explain the emphysema in asthma, since during an attack of bronchial spasm there is partial obstruction of the bronchi with hyperpnea and a prolonged expiratory phase which is not completed before another inspiration is needed, thus producing distention of the lungs and emphysema. This was apparent in our case, and the distention was so pronounced that rupture of the lung into the pleural cavity occurred. If the bronchial obstruction is complete, there is no

atelectasis or emphysema.[12] If some of the bronchi are completely obstructed, there is atelectasis in that region[11] and emphysema where the lumina are patent.

SUMMARY

A case is presented of a man of 32 with a typical history of asthma for two years. No definite allergic etiologic substance was found, but his allergy was thought to be bacterial in origin, and he apparently died of asphyxia during an acute attack. Small holes were found in both lungs with an escape of air into the pleural cavities, but without collapse of the lungs. The histologic picture in the lungs is characteristic of that described in athmatics, the chief findings being in the bronchioles: Plugging of the narrowed lumina of the bronchioles with thick mucous containing many eosinophils and Curschmann's spirals; great infolding of the mucosa of the bronchioles; a thickened hyalinzed basement membrane; hypertrophy of the muscle wall; and infiltration of the mucosa, submucosa and mucous glands with many eosinophils and plasma cells. The tracheal mucosa contains a similar infiltration. There are also marked emphysema and hypertrophy of the right ventricle.

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A SOLUBLE SPECIFIC CARBOHYDRATE OF RAGWEED POLLEN*

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MUCH work has been done in the past few years showing the presence of polysaccharides in bacterial[1] and, indeed, in other substances.[2] This, together with the evidence accumulating that these complex sugars are specific for the type of organism from which they are derived and may show antigenic activity,[3] has stimulated investigation in a new direction. It has been suggested[4] that the active substance in pollen may be other than protein, and the present investigation has been made in the attempt to discover whether a polysaccharide may be found in pollen; if this polysaccharide shows evidence of specificity and if it may act as an allergen or atopen.

METHOD

The technic reported by Ando[5] was used because of its simplicity. Some modification was made to care for different conditions.

Fifty grams *Ambrosia trifida* (giant ragweed) pollen were added to 2 liters of distilled water and allowed to stand overnight at room temperature. It was then filtered through paper, and to the filtrate were added 1.4 volumes alcohol. This was then placed in the refrigerator overnight. The precipitate was centrifuged off and dissolved in 500 c.c. physiologic salt solution, to which had been added glacial acetic acid to bring it to P_H 4.4. This was placed in the refrigerator overnight. The precipitate was centrifuged off and discarded. To the supernatant fluid were added 1.4 volumes alcohol. After standing overnight in the refrigerator the precipitate was separated and again dissolved in acid saline solution. These alternate solutions and precipitations with acid saline and alcohol were repeated five times. After the last alcohol precipitation the precipitate was centrifuged off and evaporated to dryness. It was then redissolved in saline, the reaction adjusted to P_H 7.0, placed in a dialyzing sac and covered with toluol. Dialysis against 500 c.c. distilled water was continued for two days. It was then removed and evaporated to dryness. The mass obtained consisted of a gray-white emorphous material which weighed 0.3425 gm. This was dissolved in 70 c.c. saline solution (P_H 7.0) and this solution was used for the chemical and allergic tests.

*This work was done under a grant from the Committee on Scientific Research of the American Medical Association.

CHEMICAL CHARACTERISTICS

No precipitate was obtained with picric, tannic and phosphotungstic acids, neutral lead acetate and sodium tungstate. The biuret, Millon and xanthoproteic reactions were absent. Molisch reaction was positive. Methylene blue was reduced. Potassium permanganate was slowly decolorized. Fehling's reaction was faint. After hydrolysis Fehling's reaction was quite marked. Hydrolysis yielded 55 per cent reducing sugar. Nitrogen content was 6 per cent.

TABLE I

	RAW POLLEN EXTRACT	POLYSACCHARIDE SOLUTION
Skin reaction in ragweed-sensitive	+	+
Skin reaction in ragweed-non-sensitive	–	–
Nasal reaction in ragweed-sensitive	+	+
Nasal reaction in ragweed-non-sensitive	–	–
Highest dilution giving reaction to scratch test	1– 5,000	1– 15,000
Highest dilution giving reaction to intradermal test	1–40,000	1–240,000
Highest dilution giving reaction to intranasal test	1– 400	1– 400

ALLERGIC REACTIONS

Using a 1-500 dilution, typical skin reactions were obtained in 43 ragweed-sensitive persons by both the scratch and the intradermal method. No reactions were obtained in 50 non-sensitive individuals. The activity of the polysaccharide exceeds that of the extract of raw pollen as is shown in Table I. The "point of extinction" is three times as high when the scratch technic is used and six times as high by the intradermal method. (These figures are averages of results obtained on eight ragweed-sensitive persons.) When dropped into the nose of a ragweed-sensitive person (JHB) in 0.1 c.c. amounts, the polysaccharide solution and raw pollen extract were found to be equally active. Both produced slight irritation in a dilution of 1-500, while a 1-400 dilution caused prompt sneezing, rhinorrhea and edema of the nasal mucosa.

The specificity of the skin reaction produced by the polysaccharide was absolute so far as the botanical group is concerned. No reactions were obtained in those who failed to react to one or more ragweed pollens. Marked reactions were obtained in all persons showing reaction to *Ambrosia trifida*. However, two persons who gave marked reaction to the extract of *Ambrosia elatior* (common ragweed) and very faint reaction to *Ambrosia trifida*, gave marked reaction to the polysaccharide solution.

As a check on this method of securing the polysaccharide, the work was repeated using the method proposed by Heidelberger, Sia and

Kendall.[6] The results were practically the same, the only difference being a reduction of the nitrogen content to 5.2 per cent. Allergic tests with this material have not been studied quantitatively but qualitatively are identical with those previously described.

SUMMARY

Evidence is presented showing the presence of a complex carbohydrate in ragweed pollen. This substance reacts specifically in the skin and nasal mucosa of ragweed-sensitive individuals.

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"PHYSICAL ALLERGY." REPORT OF A CASE WITH SUCCESSFUL TREATMENT*

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THE following case seems of interest because of the ease with which relief of symptoms was secured.

CASE REPORT

M. F., woman age 53 years, a superintendent in an electric lamp factory, entered Barnes Hospital December 15, 1930.

Chief Complaint.—Hives.

Family History.—There is a definite history of cardiovascular disturbances. One brother and one sister died of paralytic stroke. There are other cases of such paralyses in more remote relatives. No history of any allergic trouble.

Past History.—Patient had the usual childhood diseases including diphtheria and scarlet fever. No complications from these. She has had frequent sore throats until four years ago, when the tonsils were removed. The patient has known that she has had a high blood pressure for the past four or five years. This was discovered quite incidentally. She has had none of the usual complaints referable to this. There is no past history of allergic disturbances.

Present Illness.—For the past twenty-five years at least, the patient has been constantly subject to hives. In the beginning there was merely a persistent itching of the skin, which lasted probably for a year or two and then a definite wheal formation began to occur. This, ever since, has been constantly induced whenever the patient indulged in exercise or became overheated. For the first several years, hives would occur only on fairly vigorous exercise, but for the last fifteen years these came on with only moderate exertion, such as raking leaves, walking briskly and on similar activities. Moreover, if the patient became at all warm from exertion or even from being heavily clad, or from too many blankets at night, she would break out into an urticarial eruption. She could never bathe in water that was more than lukewarm. Hives occurred at no time other than during exertion or excessive warmth. Skin tests were attempted about a year ago and the patient responded to everything injected. During the hot summers in St. Louis the patient has always suffered from hives quite severely. She maintains, however, that she rarely perspires. Her

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eruption itches and burns. Other than chronic constipation, no other symptoms are complained of.

Physical Examination.—The positive findings were as follows: The skin was quite dry and clear. No eruptions were noted. On stroking the skin, however, a moderate dermatographism appeared. The ophthalmologic examination showed some sclerotic changes in the retinal arteries. A mild degree of emphysema was present. The heart was slightly enlarged to the left; the borders were uncertain because of emphysema. The sounds were of good quality; A 2 greater than P 2. A soft systolic murmur was heard at the aortic area and transmitted toward the neck. Blood pressure 178/94. Remainder of the examination was negative.

Laboratory Findings:

RBC ..... 4,570,000.
Hemoglobin ..... 94 per cent.
WBC ..... 7,900.
Schilling Differential Count ... Normal (but 1 per cent eosinophiles).
Uranalysis was essentially negative.
Gastric analysis by the fractional method showed free hydrochloric acid and there were no abnormal findings.
The blood nonprotein nitrogen was ..... 26 mg. per cent.
The blood sugar was ..... 107 mg. per cent.
The blood Kahn test was negative.
The basal metabolic rate was ..... +6 per cent.
The electrocardiogram was normal.
Skin tests were not possible because of dermatographism.

The patient's tolerance to exertion was tested by various exercises. After brisk walking for four minutes she complained of a generalized itching of the skin and within a few minutes an eruption of small urticarial wheals occurred all over the body excepting the face, where but few appeared. Calisthenic exercises produced the same result. The eruption and itching lasted from thirty to forty minutes. An identical effect was produced within half an hour after the patient was covered with several blankets. Wheals occurred almost immediately after immersion in a hot tub.

The following régime was then instituted. The patient was instructed to remain under a warm shower bath for five minutes. She did this at home and was not observed. Her report was that an intense urticarial eruption appeared almost immediately. She felt faint and nauseated for a short time afterward. The process was repeated the following day, and the eruption was decidedly less with no constitutional symptoms. Daily shower baths with gradual increase of the water temperature and a lengthening of the time of immersion caused a complete disappearance of symptoms within one week. The patient

could then remain under a hot shower for one half hour without the slightest discomfort, and no reappearance of the eruption. The showers were discontinued after three weeks. About ten days later a generalized itching of the skin returned without wheal formation. This was not associated with exercise or excessive warmth. The baths were resumed and the patient has been symptom-free for the past six weeks. She is able to indulge in as much activity as she wishes and overheating causes no discomfort.

DISCUSSION

Duke,[1] Horton and Brown[2] and others[3] have reported cases of so-called "physical allergy." In these cases, skin manifestations characterized by localized edema or a generalized urticarial eruption have occurred. There is a distinct clinical difference between these two types of reaction. In the localized form, the exposure of a single part, such as the immersion of the hand in cold water will cause localized swelling, redness and burning, followed at times by constitutional reactions. These include faintness, fall in blood pressure with dizziness and a diffuse flushing. The generalized eruption occurs particularly in the heat- and effort-sensitive patients. The difference between the localized and generalized types of reaction is apparently one of degree as the same underlying cause seems responsible for each.

In the case here reported it is evident that the factor underlying the symptoms was identical for exercise and overheating. This is the general rule in this type of case. Horton and Brown have indicated in their cases of allergy due to cold, that symptoms were caused by release of histamin or of some substance with a histamin action from the skin. This is in keeping with Lewis and Grant's[4] demonstration of such a substance which they believe causes wheal formation in urticaria factitia. Recently Holzapfel[5] has shown that in a case of factitious urticaria repeated stroking of the skin released a histamin-like substance (not histamin) which could be recovered in the blood stream.

Of particular significance is the demonstration by Mackenzie and Baldwin,[6] Storm van Leeuwen[7] and others that the capacity of the skin for reproducing a positive allergic reaction becomes exhausted after repeated injections of the specific allergen at the same site.

Török likewise showed that when histamin is repeatedly introduced into one site of normal skin there is first an increase and then a gradual diminution of wheal formation. Horton and Brown relieved three of their six cases of cold allergy by exposure to increasingly lowered temperatures. Duke mentions the value of such treatment. Henry[8] reported the case of a man with effort-sensitiveness who, after forced violent exercise, became relieved of symptoms.

It appears then, that under various circumstances the skin of certain individuals has the capacity of elaborating a histamin-like substance in

excessive amounts. This induces localized swellings on the skin. It is possible to exhaust the mechanism underlying this process and treatment is based on this fact. The case here reported secured relief in a much shorter period than most of the cases recorded.

SUMMARY

A 53 year old woman had been subject to hives for the past 25 years. These came on after moderate exertion and overheating. Physical examination revealed a moderate arterial hypertension, and a dermatographism which did not permit skin tests. The patient's tolerance to exertion and excessive warmth was determined and found to be low. From data available from experiments and from treatment of a few similar cases reported, it was inferred that the mechanism underlying urticarial production could be exhausted. The patient was, therefore, subjected to immersion in warm water. This was followed by an intense urticarial eruption. The water temperature and length of immersion were gradually increased and symptoms correspondingly diminished until the patient finally became tolerant to heat and exercise and experienced no further symptoms.

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STUDIES ON POLLEN AND POLLEN EXTRACTS

II. THE ADSORPTION OF ALLERGICALLY ACTIVE CONSTITUENTS FROM POLLEN EXTRACTS*

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WHILE some studies have been made with the purpose of purifying and identifying the active constituent or constituents from various kinds of hay fever producing pollen, the results are not conclusive. The different fractions prepared by the usual means of protein separation[1, 2, 3, 4, 5, 6, 7, 8] and the material extracted by fat solvents[9] have all been found reactive by skin-test methods. There is disagreement as to whether or not the active material is protein in nature.[10, 11, 12, 13, 14]

It occurred to us that it might be possible to find an adsorbent which would preferentially remove the active material from a pollen extract. This should prove an efficient means of purification and give a clue to the nature of the material responsible for allergic activity.

During the progress of this work, a paper by Stull, Chobot and Cooke[15] appeared. These authors report unsuccessful attempts to adsorb the active material from pollen extracts. The discrepancy between their results and those to be described in this paper is probably due to different technic in preparation of extracts and adsorbents.

METHODS AND RESULTS

I. *Chemical Study.*—The pollen extracts used were prepared by treating 20 grams ether-extracted pollen with 200 c.c. extracting menstruum. Redistilled ammonia-free water and Coca's saline solution (5 gm. NaCl and 2.7 gm. $NaH\ CO_3$ per liter) were used as extracting fluids. The liquid was well shaken with the pollen and allowed to stand overnight at about 2° C., after which it was filtered by suction through a hardened paper. The extracts were preserved by a layer of toluene.

The adsorbents used were commercial preparations of active charcoal, diatomaceous silica and silica gel, and gels of alumina and iron oxide prepared in this laboratory. The adsorbents were all passed through a 100-mesh sieve and dried at 120° C. for several days before use.

Twenty c.c. samples of each extract were treated with 1 gram of adsorbent for at least twenty-four hours, and the liquid was then filtered by suction, using a Gooch crucible and a hardened filter paper.[16]

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For determinations of total solids, 5 c.c. samples were withdrawn from the original extract and from each of the solutions after adsorption. These were dried at 110° C. and weighed as "total solids," and were finally ignited and the weight of ash was determined. The latter showed that no appreciable amount of adsorbent passed through the filter. In case of the alumina and iron oxide, the ash was considerably less in the solution after adsorption than in the original.

For nitrogen determinations, 1 c.c. samples were used, and the analysis was carried out by the micro-Kjeldahl direct Nesslerization method of Koch and McMeekin.[17]

The analytical results are shown in Tables I and II.

TABLE I

ADSORPTION FROM GIANT RAGWEED POLLEN EXTRACT

EXTRACTING FLUID	ADSORBENT	TOTAL SOLIDS MG. PER C.C. REMAINING	TOTAL SOLIDS MG. PER C.C. REMOVED	TOTAL SOLIDS % REMOVED	ASH MG. PER C.C.	NITROGEN MG. PER C.C. REMAINING	NITROGEN MG. PER C.C. REMOVED	NITROGEN % REMOVED
Water		16.10			1.45	0.94		
Water	Silica Gel	15.54	0.56	3.48	1.65	0.90	0.04	4.26
Water	Diatomaceous Silica	15.94	0.16	0.995	1.5	0.86	0.08	8.52
Water	Active Charcoal	9.58	6.52	40.5	1.5	0.475	0.465	49.5
Water	Alumina Gel	12.26	3.84	23.8	0.99	0.814	0.126	13.4
Water	Iron Oxide Gel	10.10	6.00	37.3	0.69	0.58	0.36	38.3
Saline		23.94			4.3	1.08		
Saline	Silica Gel	22.30	1.64	6.85	4.1	0.93	0.15	13.9
Saline	Diatomaceous Silica	23.84	0.10	0.418	3.6	1.05	0.03	2.78
Saline	Active Charcoal	14.60	9.34	39.0	4.3	0.42	0.66	61.1
Saline	Alumina Gel	20.40	3.54	14.8	2.8	0.89	0.19	17.6
Saline	Iron Oxide Gel	18.54	5.40	22.6	2.4	0.81	0.27	25.0

TABLE II

ADSORPTION FROM TIMOTHY POLLEN EXTRACT

EXTRACTING FLUID	ADSORBENT	TOTAL SOLIDS MG. PER C.C. REMAINING	TOTAL SOLIDS MG. PER C.C. REMOVED	TOTAL SOLIDS PER CENT REMOVED	ASH MG. PER C.C.	NITROGEN MG. PER C.C. REMAINING	NITROGEN MG. PER C.C. REMOVED	NITROGEN PER CENT REMOVED
Water		32.70			2.9	1.19		
Water	Active Charcoal	25.82	6.88	21.0	2.4	0.563	0.627	52.7
Water	Iron Oxide Gel	29.11	3.59	11.0	1.8	0.97	0.22	18.5

II. *Clinical Experiments:*

1. Tests on Naturally Sensitive Individuals.—Certain filtrates after adsorption were tested on patients sensitive to the whole ragweed pollen extract, using the scratch method of skin testing. The number of such tests is too small to be conclusive, as only sixteen patients were available for this work and all the solutions were not tested on every patient. In every case tested, the solution after adsorption with the diatomaceous silica gave definitely positive reactions in sensitive pa-

tients, while in no case was a reaction provoked by the filtrate after adsorption from the water extract with active charcoal. The results of tests with filtrates from alumina adsorption were variable. Tests with the iron oxide and silica gel filtrates both gave definitely positive reactions.

Tests with the dried solid charcoal after adsorption were not always positive, but this may be merely quantitative. The method of testing was addition of a drop of water to a small portion of the solid just before scratching. This procedure could not be expected to give a very great concentration of the active material in contact with the tissues. No positive reactions were observed from the dried alumina adsorbent.

2. Tests on Passively Sensitized Sites in Humans.—The solutions used for chemical analysis, diluted 1:10 with physiologic salt solution, were tested for activity by the intradermal method in sites on normal individuals sensitized by local passive transfer with the serum of sensitive patients.[18] Four different normal subjects were used for these tests, and in most cases the serum of a patient sensitive to both timothy and ragweed pollens was used for passive sensitization of the skin sites. In a few of the tests the serum of a patient sensitive only to ragweeds was used. This method is most satisfactory for routine testing of solutions, because the sites are readily available when needed if a supply of sensitive serum is at hand.

By this means we were able to establish the fact that the activity of water or saline extracts of ragweed pollen is not decreased by treatment with the silica gel or diatomaceous silica. Adsorption with gels of alumina or iron oxide appears to cause a definite decrease in activity of water or saline extracts, but the concentrations used here did not completely remove the activity. This decrease in activity apparently does not consist in the preferential removal of one antigen as might be suspected from the erratic behavior of the alumina filtrate on hay fever patients, for sites exhausted to either the alumina or iron oxide filtrates gave no further reaction to saline extract of whole pollen. Iron oxide seemed more effective than alumina in decreasing activity as measured by the extent of reaction in passively sensitized sites. In the case of the water extract of timothy pollen, the activity was much decreased by adsorption with iron oxide.

The active charcoal was found to be most efficient as an adsorbent for the allergically active substance in the water extract of giant ragweed or timothy pollen. The skin-reacting substance could be completely removed, as measured by tests on passively sensitized local sites. The effect of hydrogen-ion concentration is quite marked, and adsorption is much less from the saline extract of P_H 8.4 than from the distilled water extract of ragweed pollen. When the charcoal ad-

sorbent from the water extract is washed with Coca's saline solution, the resulting filtrate causes a reaction in sensitized sites.

III. *Animal Experiments.*—In order to test the similarity of reactions in humans and in sensitized animals, certain of the solutions after adsorption were tested on rabbits immunized to the whole pollen. The trypan blue skin reaction method of Ramsdell,[19] as applied in this laboratory to pollen-sensitized animals,[20] was used for these tests.

Each of five rabbits tested, sensitive to ragweed pollen extract, gave positive reactions to the solution from adsorption with the diatomaceous silica. Four rabbits were tested with filtrates from the iron oxide and silica gel adsorbents, and one rabbit was tested with the filtrate from alumina adsorption. Positive reactions ensued in all cases. Three negative tests and one doubtful reaction resulted from tests with the solution after active charcoal adsorption.

In two tests with timothy-sensitive rabbits, two positive reactions were elicited by the filtrate from diatomaceous silica adsorption. In the single test with the solution from adsorption with alumina gel, a positive reaction was obtained.

The charcoal used for adsorption from the water extract of timothy pollen (2 grams charcoal in 40 c.c. extract) was dried and divided into five approximately equal parts. Each of these was then extracted overnight with 5 c.c. of one of the following solutions:

	SALTS IN SOLUTION	P_H	INDICATOR
(1)	$Na_2HPO_4 + KH_2PO_4$	7.0	Phenol Red
(2)	$NaHCO_3$	8.4	Thymol Blue
(3)	Na_2HPO_4	8.5	Thymol Blue
(4)	Coca's Saline	9.0	Thymol Blue
(5)	$Na_2CO_3 + NaHCO_3$	9.6	Thymol Blue

When these solutions, diluted 1:10 with physiologic salt solution, were tested in the skin of a timothy sensitive rabbit, only the Coca's saline extract gave a definitely positive reaction. This was not as deep blue or as large as the reaction with the whole water extract of timothy in the same dilution.

DISCUSSION

The agreement between the tests on sensitized animals and on naturally sensitive or passively sensitized human subjects is seen to be remarkably good. The experiments strongly suggest that the active material in the two instances must be similar if not identical, as it is apparently preferentially adsorbed by the same agents.

The order of activity, by clinical and animal tests, closely parallels the percentage of solids and of nitrogen removed, according to the chemical analysis. However, in the ragweed pollen solution which showed no activity after charcoal adsorption, more than half the total solids and approximately half the nitrogen were still present. From

the timothy pollen extract only about 7 per cent of solid material and half the nitrogen were removed by active charcoal. These results show that the allergen must be considerably concentrated on the adsorbent. Investigations are now being carried out in this laboratory of the optimum conditions for removal of this concentrated active material from the adsorbent.

SUMMARY

1. The efficiency of five different adsorbents for solid materials and for nitrogen from two giant ragweed pollen extracts, has been measured. The extracts used were ones commonly employed for clinical desensitization, water and a buffered saline solution serving as extracting fluids. The same determinations have been made on a water extract of timothy pollen, using the two most efficient of the above adsorbents.

2. The activity of extracts and of filtrates after adsorption was tested:

(1) By the scratch method on hay fever patients sensitive to the whole pollen extract.

(2) By the intradermal method in sites on normal individuals sensitized by the method of local passive transfer

(3) By skin tests on rabbits sensitized to the whole pollen.

3. The order of efficiency as measured by chemical means was the same as that measured by the skin-reacting activity of the filtrates after adsorption, toward humans or sensitized rabbits. This order was: active charcoal, iron oxide and alumina gel, diatomaceous silica and silica gel. The last two adsorbents appeared to cause no decrease in activity of the extracts.

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THE TOXIC FRACTION IN CERTAIN ECZEMA SERUMS*

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ALTHOUGH a brief report of this study has already appeared,[1] I feel that it will bear repetition and enlargement in relation to the passive transfer of the allergic skin test.

Toxicity as measured by an immediate response to serum injected intracutaneously has been reported by Gay and Chant.[2] These investigators found that heating blood serum at 56° C. for thirty minutes or more caused a definite and immediate reaction on intracutaneous injection. Similar positive reactions were obtained with serum kept at ice-chest temperature for twelve days or more.

Our attention was called to this phenomenon by the occurrence of immediate reactions while studying passive transfer phenomena of infantile eczema serum. Certain of these were of such noticeable intensity that steps were taken to control the observation.

Method.—Blood was drawn aseptically before a feeding from infants with eczema. It was allowed to clot at room temperature and the serum was separated by centrifugalization. The serum was then removed by sterile pipette and transferred to a small sterile bottle with rubber cap. After being tested for sterility, small amounts were removed for injection as needed.

Besides controlling the factor of bacterial contamination the method safeguarded against the factors previously known to effect the reaction. Serum was not used immediately after clotting. It was not heated, nor kept on ice for longer than twenty-four to forty-eight hours.

In spite of these precautions, certain of the serums gave immediate reactions. We then considered the following possibilities:

1. Circulating antigen in the blood of the recipient. This was to be considered since the serum was from infants sensitive to foods in the common dietary and since it was possible that sufficient antigen might be present at the time of injection to give an immediate response.

2. A difference of blood group of donor and recipient. Nothing definite was known about the effect of blood groups on the reaction to intracutaneous serum injection, but in view of their effect in transfusions, etc., it was considered possible that an incompatibility would produce some variation in response.

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3. The effect of extensive skin injury. In view of Lewis and Harmer's[3] work on a toxic "histamine-like" substance released from injured skin cells, a nonspecific toxin arising from various types of skin injury was thought possible.

Accordingly, experiments were designed to test these three possible factors. Recipients for the passive transfer were selected, representing the four blood groups. Tests were made after the recipients had fasted and also on infants whose diets had never included the foods to which the donor was sensitive.

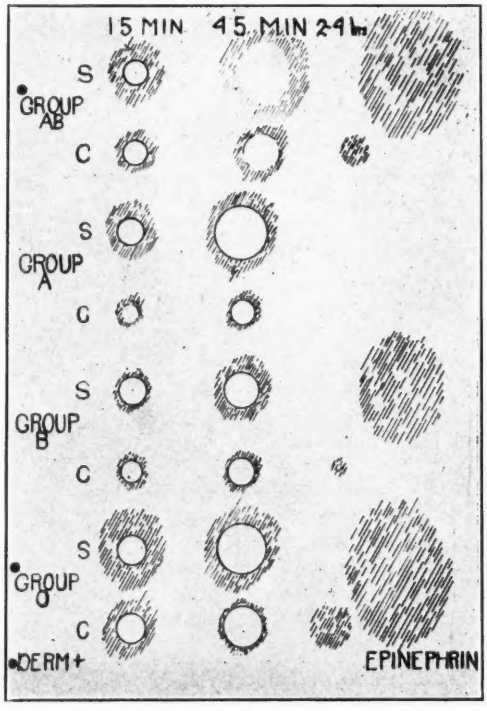

Fig. 1.—Group A = Moss group 1. Group B = group 2. Group AB = Moss group 3. Group O = Moss group 4.
S = reaction from the patient's serum.
C = reaction from the control serum.
O = a heightened response of the recipients skin to trauma, i. e., dermatographia. Epinephrin injected because of the intensive edema was without effect. This initial reaction subsided in all instances in twenty-four to forty-eight hours and in no way influenced the successful passive transfer test with intracutaneous egg albumen injection at that time.

Fig. 1 illustrates the results of injection of 0.1 c.c. of serum from an infant with eczema and with a positive skin test to egg white. The donor belonged to Group 0 (4 "Moss"), while recipients were chosen representing all four blood groups. A control serum from Group 0 was injected simultaneously. After the night's fast the recipients were injected on the flexor surface of the forearms.

To test the effect of extensive skin injury, blood was obtained from 2 patients with lichen urticatus, 3 patients with extensive burns of

the skin, 1 patient with extensive exfoliative dermatitis, and from 1 child with marked dermatographia. In the last case the blood was taken when extensive reactions had appeared after voluntary scratching. While perhaps this group was rather small, the negative results obtained point to the fact that extensive skin injury is not necessarily accompanied by the production of toxic properties in the blood serum, at least so far as can be judged by intracutaneous injection.

DISCUSSION

While Gay and Chant[4] have described the effects of heat and prolonged exposure to cold which renders even normal serum toxic for intracutaneous injection, we have found that specimens of serum from infants with extensive eczema and sensitive to certain allergens by skin and passive transfer tests, show a similar immediate toxic reaction. Walzer,[5] in a series of studies, demonstrated wheal formation at the site of serum injection when the recipient was fed foods to which the donor was sensitive. Our experiments using infants who had never been given the offending foods, as well as adults on fasting, excluded this phenomenon.

Theoretically, the skin cells might contain toxic substances which would be liberated after cell injury. Lewis and Harmer[6] have elaborated this explanation for the reaction of the skin to trauma, especially pronounced in factitious urticaria. According to his theory, trauma releases this "histamine-like" substance which is then free to act on the adjacent tissue with resultant capillary permeability, local edema, and erythema. The wheal fluid and blood do not give constant results due, it would seem, to the dilution of the "histamine-like" toxin. In factitious urticaria there may be a general reaction (manifested by lowering of blood pressure, etc.) while the normal shows only the local reaction.

Since our initial observations on the phenomenon reported here, Alexander[7] has studied the effects of skin extracts injected intracutaneously. He finds an augmentation of the reaction to histamine injection when a water-soluble skin extract is added to the histamine. Our experiments using serum from patients with extensive skin injury other than eczema, failed to show any such toxin. That there may be a question of dilution of the substance must also be borne in mind, though at present we cannot conclude that the substance results from nonspecific skin injury.

SUMMARY

On intracutaneous injection, the serums from certain infants with eczema give an immediate wheal formation. In about 30 patients with eczema, studied by passive transfer, 10, or over 30 per cent, showed this phenomenon. This toxicity is not related to enteral absorption

of offending allergens nor to alteration of the colloidal properties by heat or cold. It resembles the effect of the theoretical "histamine-like" substance described by Lewis in studying the response of the skin to trauma, but other conditions in which there was extensive skin injury failed to show similar toxicity in the serum.

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A STUDY OF THE ALLERGIC SKIN-TEST SUBSTANCE*

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TO OUR knowledge no previous attempts at purification of the substance responsible for the skin-test phenomena of allergic conditions have been reported. In view of the fact that the serum from an individual with positive skin tests could sensitize a normal skin, it seemed logical that the essential fraction of the serum could be separated if not purified. The experiments reported here were directed toward such a study.

Samples of serum were kept for as long as nine months without apparent loss of their sensitizing power. Samples of serum dialyzed against distilled water for a week, after which they were passed through a Berkefeld filter, were still potent. The destroying effect of heat at 56° C. previously reported by Gay and Chant[1] was likewise verified. Experiments were also carried out to see whether contact with red blood cells of the same or different blood group as the donor, would affect the essential fraction of the serum. Washed cells suspended in the serum and incubated had no appreciable effect on the sensitizing power of the serum. This was quite compatible with the fact that the substance behaved as a colloidal protein and was nondialyzable, but affords a contrast with the lysin associated with hemoglobinuria and urticaria from cold which Harris, Lewis and Vaughan[2] showed was adsorbed by red blood cells.

Separation of the albumin and globulin fractions was then attempted by the following means:

I. Saturation with carbon dioxide
II. Precipitation of globulin with dilute hydrochloric acid
III. Precipitation of globulin with saturated ammonium sulphate.

I. Ten c.c. of serum from a patient whose serum had been successfully used for passive transfer were diluted with 190 c.c. of sterile distilled water. This was chilled in an ice bath, and carbon dioxide was passed through the mixture until no further precipitate formed (about forty minutes). The precipitate, separated by centrifuge, was then dialyzed against the buffered saline solution used by Coca and Milford.[3]

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After forty-eight hours most of the precipitate had redissolved, and it was made up to 10 c.c. volume with Coca's solution. The albumin (filtrate fraction) was passed through a Berkefeld filter and evaporated with the aid of an electric fan to approximately 10 c.c. in volume. After a second passage through a Berkefeld filter, this fraction was likewise ready for testing. Two satisfactory recipients were used but passive transfer with either fraction was negligible.

II. Precipitation with hydrochloric acid: This method has been used by Fujimoto[4] in the study of the antitrypsin of serum. To 5 c.c. of serum 40 c.c. of N/250 hydrochloric acid were added. The mixture was allowed to stand for two hours, during which a flocculent precipitate accumulated. By centrifuging the precipitate was readily separated. Dialysis was carried out as before. The albumin fraction was concentrated to 10 c.c. and treated in a similar manner. After passing through the Berkefeld filter both fractions were used for passive transfer. The globulin fraction gave weak positive reactions.

III. To 5 or 10 c.c. an equal volume of saturated ammonium sulphate was added. After two to four hours standing the flocculent precipitate had settled sufficiently to allow separation by centrifuging. Both precipitate and filtrate were transferred to cellophane bags. Dialysis was accomplished by a two-stage process, i.e., six hours dialysis against distilled water and two days dialysis against the buffered saline solution. The solutions were then practically free of ammonium sulphate and after passage through the Berkefeld filters were suitable for testing.

Table I shows the comparative strength of the various fractions studied.

TABLE I

SUBSTANCES		REACTION I	CONTROL	REACTION II	CONTROL
Original Serum		20 × 30	5 × 5	20 × 20	3 × 5
HCl	precipitate	10 × 10	5 × 5	8 × 10	5 × 5
	filtrate	5 × 5	5 × 5	3 × 5	3 × 5
CO_2	precipitate	5 × 5	5 × 5	5 × 5	5 × 5
$(NH_4)_2SO_4$	precipitate	30 × 40	5 × 5	30 × 30	3 × 5
	filtrate	5 × 5	5 × 5	3 × 5	3 × 5

The results were so striking that it seemed desirable to investigate further the uses of the ammonium sulphate separation method. After parallel results from the globulin fraction of three other serums giving satisfactory passive transfer, serum was obtained from individuals giving weak skin tests and unsatisfactory transfer. In two such cases the globulin fraction gave a stronger passive transfer than the original serum. Fractions of serum preserved for some time in the ice chest were likewise treated with the ammonium sulphate, and it seemed to us that purification was better in this instance, possibly because of the separation of the lipoidal matter.

That tissue extracts might likewise contain essential globulin was next considered. Red blood cells were separated from oxalated blood samples as well as from the clot where serum had been used. The serum from these patients had proved satisfactory for passive transfer. The cells were washed three times by centrifuging with normal salt. They were then hemolyzed with distilled water, and the globulin was precipitated with ammonium sulphate. Dialysis and filtering through Berkefeld filter was carried out as with the serum globulin. This fraction was inert so far as passive transfer was concerned.

Tonsil tissue was obtained after operative removal from two patients with serum satisfactory for passive transfer. This tissue was cut in small fragments and ground with sand in a mortar. The finely ground mixture was then shaken for two hours with buffered salt solution. After centrifuging, the supernatant fluid was treated with ammonium sulphate. Considerable precipitate was formed which was then carried through the routine dialysis and filtering through Berkefeld candles. When used for passive transfer the extract was inert. Although we have by no means exhausted the study of tissue extracts, it has been so far impossible to demonstrate the essential fraction in tistues other than the blood serum or plasma.

DISCUSSION

The antitryptic fraction of serum has been studied by Fujimoto.[4] By precipitation with ammonium sulphate, the globulin and albumin were both found antitryptic, although the globulin was less patent than the albumin. The fraction was nondialyzable. Ether extracts were inert.

In the study of experimental anaphylaxis, the fraction of the serum which transferred sensitivity from a sensitized to a normal animal was found by Sleeswijk[5] to be retained when the serum was dialyzed against water. Doerr and Russ[6] found that this fraction was precipitated with the globulins.

It has been known for some time that antitoxin may be precipitated with the globulin of horse serum. Gibson[7] was able to purify diphtheria antitoxin by precipitation with ammonium sulphate. By obtaining the pseudoglobulin at the height of its increase during immunization, he was able to obtain an increase of 40 to 100 per cent. Banzhaf[8] also showed that heating the antitoxic serum for six to eight hours at 56° converted about 30 per cent of the pseudoglobulin to euglobulin. By heating in the presence of 30 per cent saturated ammonium sulphate, the euglobulin removed by precipitation as it formed allowed further conversion of the pseudoglobulin to euglobulin. This resulted in a highly potent antitoxin bearing pseudoglobulin. Separation of the lipoidal substances which interfere further with the purity of the antitoxin, occurred on standing in cold storage for three to four months.

Dealing as we were with only small amounts of human serum, the complete separation of the nonessential euglobulin was prohibited. It was also known that heating at 56° C. was injurious to the antibody we were studying. However, by application of Banzhaf's[9] later method using saturated sodium chloride as well as 35 per cent saturated ammonium sulphate we precipitated small amounts of euglobulin and lipoids. The only modification necessary to Banzhaf's method was the avoidance of heat destruction of the substance being studied. Sufficient amounts of the euglobulin fraction were obtained to contrast with the pseudoglobulin and they were judged inert. This we felt was necessary, since it is known that the antitoxin fraction may vary with species as to its association with the euglobulin or pseudoglobulin. As to the lipoidal substances, we found apparently better yields of the antibody if the serum had been stored for some time in the cold rather than treated when fresh.

SUMMARY

Treating the serum from patients giving positive skin tests with saturated ammonium sulphate, the essential antibody fraction is precipitated with the globulins. The albumin fraction is without sensitizing power, as judged by passive transfer, while the precipitated globulins when dialyzed and redissolved are potent. While passive transfer offers a poor means of estimating the titer of this antibody, it is apparently possible to concentrate the substance. It is found associated with the pseudoglobulin,* not with the euglobulin, and the nonessential lipoidal substances may be eliminated by prolonged cold-storage of the serum before treatment with ammonium sulphate. In many respects the antibody substance behaves like the antitoxin of diphtheria, save in its relative heat lability.

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*We use the term "associated with pseudoglobulin" feeling that the exact chemical nature of antibodies is still a matter of discussion.

STUDIES IN PASSIVE TRANSFER*

FRANCIS SCOTT SMYTH, M.D., SAN FRANCISCO, CALIF.

AND

KATHERINE BAIN, M.D., ST. LOUIS, MO.

SENSITIVITY OF RECIPIENTS

WHEN we began using the method of passive transfer routinely in our studies of allergic individuals, we were surprised to find that our recipients failed to show the wide difference in susceptibility generally accepted. Coca and Grove[1] found that of 103 individuals, 12 were nonreceptive and 5 were receptive to only a slight degree. Unfortunately, these workers failed to note what serum was used and whether the same serum was employed in all the cases. Levine and Coca,[2] in studying atopic reagins in hay fever, found that of 60 recipients, 5 (8 per cent) were slightly or not at all receptive. Again, it is not stated whether those giving negative tests were retested with different sera.

Our first series of experiments was with a group of 93 children, 50 males and 43 females ranging in age from seventeen months to sixteen years. The patients were all orthopedic cases undergoing treatment, and at the time of the experiments were afebrile and in good physical condition. The serum used was from an adult sensitive to ragweed, who had typical clinical symptoms as well as a positive skin test. The serum was tested in a known recipient and gave a positive reaction. All the children were tested at one time, 0.1 c.c. being injected into the skin of the forearm, and the site tested in forty-eight hours with 0.05 c.c. of 1:100 solution of ragweed. A control using the same amount of ragweed solution was made on the opposite arm.

Of the 43 girls tested, 31 gave marked reactions, 3 showed erythema but no wheal, and 9, though giving a good reaction, showed some redness at the site of the control. Those giving weak or confusing reactions were retested, using egg-positive serum. Of the 9 giving some reaction at the site of the control with ragweed, all gave positive reactions to the egg serum, with a negative control. Of the 3 giving poor reactions before, 1 disappeared and 2 gave the same reaction—erythema, or 1-plus. Thus, there were no complete negatives in this group of 43, and only 3 with poor results.

Of the 50 boys tested with ragweed serum, 37 gave a 4-plus reaction, 1 erythema only, and 12 showed a positive control. When retested with egg-positive serum, a strongly positive test was obtained on the

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individual giving erythema previously, and of the 12 showing positive control, 9 gave a 4-plus reaction with negative control and 3 were lost. Eliminating from both groups those that were lost, from a total of 89 children only 2 gave a small reaction and none was negative.

The next group consisted of 35 children ranging in age from five to fourteen years, 19 males and 16 females, all convalescent medical patients. These were tested with egg-positive serum. Four gave reactions ranging from erythema to 1-plus. The remainder gave good positives. The 4 giving weakly positive tests were later retested with egg-positive serum of much higher titer, and gave 4-plus reactions. This serum was obtained from an infant (Calahan) fifteen months of age, with a 3-plus skin test to egg and moderately severe asthma following ingestion of egg. The serum, however, had a reagin titer far in excess of the clinical manifestations.

The third group consisted of 50 newborn infants all injected with the same egg-positive serum (Calahan) and all tested with 1:100 solution of egg white, prepared according to Coca. There were no failures in this group.

In order to eliminate all the factors which might operate in inhibiting passive transfer, the possibility of the effect of the blood group was considered. The accompanying table shows the result of transfer in relation to blood group:

CHART I

THE RESPONSE TO PASSIVE TRANSFER OF RECIPIENTS WITH DIFFERENT BLOOD GROUPS TO THE SERUM OF DONORS WITH FIXED BLOOD GROUPS

DONORS		RECIPIENTS			
NAME	GROUP	GROUP O	GROUP A	GROUP B	GROUP AB
Crowe	A	++++	0		
Finley	O	++++	++++	++++	
Freese	O	++++		++++	++++
Gmoser	B	++++		++++	

The first patient, Crowe, was an infant five months old, who had never eaten egg but had a skin test 4-plus to egg white. The titer of this serum was probably rather low, since the recipient in Group A gave a good reaction with a stronger serum. All the positive reactions were approximately the same size. Apparently transfer is unaffected by blood group.

It may be seen that of the possible variations causing a poor reaction to passive transfer, sex is of no importance. An age range from one day to sixteen years with no preponderance of negatives in any one group, should eliminate age as a factor. It would seem from a study of these groups that the variation is not so much in the recipient as in the serum used. Although it may be true that about 85 per cent of

all skins will be susceptible to any serum, if a different serum is used or one of higher titer, a good response will be obtained from those previously negative. This is suggested by Levine and Coca,[3] who found that in a group of 35, 86 per cent were negative to dust serum, but that the remainder could be sensitized by a different serum. Also, that of another group, those who could not be sensitized to timothy could be sensitized to ipecac.

TRANSFER TO NEWBORN INFANTS

The series of 50 newborn infants mentioned in the previous sections, requires some elaboration. The type of reaction obtained on the skin of a newborn infant differs from that obtained on an older child or an adult. In the newborn infant a positive reaction is not difficult to obtain, provided a potent serum is used, but the reaction consists of a wheal from 2 to 3 cm. in diameter, with considerable surrounding redness and some edema. The wheal is well formed but there are rarely pseudopods. In older children, however, the passive transfer test resembles the direct test—wheal, pseudopods, erythema.

No attempt was made to elicit indirect passive transfer, i.e., by ingestion, in the older children. In several cases the sensitized site showed a wheal, following a meal, but this was accidental. However, three of the newborn infants were selected for indirect passive transfer. These were given 1 to 2 ounces of 10 per cent egg albumen water, and in from fifteen to twenty minutes a wheal and considerable swelling were noticed. These cases were studied in the course of an experiment on passive transfer by means of breast milk, a report of which will be made. They are included here to show the ease with which indirect passive transfer is obtained, if a serum of high titer is used.

TRANSFER TO VARIOUS TYPES OF SKIN

The failure to obtain positive skin tests in allergic individuals has elicited a voluminous literature. It seemed pertinent to attempt to use the skin of an allergic for passive transfer. Five allergic individuals were selected, 2 of these, clinically pollen sensitive, were tested with ragweed-sensitive serum. The results obtained were identical with those of nonallergic controls. The remaining 3, clinically sensitive to foods or inhalants (but not to egg) were tested with egg-sensitive serum and gave results identical with those of the controls. Levine and Coca,[3] in a footnote, mention the series of 35 asthmatics with negative skin tests who gave the same type of response to transfer as nonallergics.

The reverse of the experiment was attempted; i.e., transfer to allergic patients with positive skin tests, in order to see whether or not there was any increase in the reactions.

Two patients sensitive to egg were selected for transfer to each other, serum of one being injected into the forearm of the other. These sites, as well as an uninjected site of each individual, were tested with a 1:10,000 dilution of egg albumen intracutaneously, and gave approximately the same results. In one the control was slightly larger than the injected site.

CORD BLOOD TRANSFER

For several years we have attempted to secure cord blood from mothers who are definitely allergic. Unfortunately, we have not been able to obtain the material. In one case, in which the mother was ragweed-sensitive, we obtained cord blood, but were unable to elicit transfer in known recipients. In several other cases where there has been a history of allergy in the family, we have obtained specimens of cord blood, which have been tested by passive transfer for reagins to milk, egg, and wheat, with negative results. We hope to obtain sufficient material to complete these experiments at some future time.

COMMENT

In general, the passive transfer phenomenon parallels that of the skin test. It is obtained with greater ease with serum from persons giving strongly positive skin tests. It has been stated by Coca and Grove[4] that atopic reagins are demonstrable by passive transfer in all persons with clinical symptoms and positive skin tests. We have not found this always the case. In two persons with positive skin tests and with typical ragweed hay fever, no reagins were demonstrable by passive transfer. It is much easier to obtain passive transfer with serum from a person sensitive to egg than from one sensitive to wheat, and with pollen-sensitizing serum, as compared with other inhalant-positive sera. But, between sera sensitive to the same substance, passive transfer is apparently dependent on the reagin titer.

From reports elsewhere we have shown that certain persons may be definitely sensitive, yet fail to show the presence or development of skin-test antibodies (reagins). From other reports the presence of positive skin tests with failure of any clinical phenomena has likewise been shown. It appears to us that while usually related, the capacity to form skin-test antibodies (reagins) and the capacity to react clinically are independent variables.

CONCLUSIONS

1. Of 174 children used as recipients for passive transfer, 8 gave poor reactions. When these were retested with serum of high titer, only 2 gave poor reactions. (These were not tested with the most potent serum obtainable.)

2. Sex, age, and blood group are not factors in the variation of the recipient.

3. Passive transfer to newborn infants is obtained with ease, but the reaction produced is a wheal without pseudopods.

4. Passive transfer is not increased when the recipient is an allergic individual with positive tests, nor is it decreased if the recipient is allergic with negative tests.

5. The chief factor causing variation in the production of passive transfer is the titer of the serum.

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URTICARIA DUE TO GRASS POLLEN*

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CHICAGO, ILL.

AS IS well known, urticaria is believed to occur as a result of the action of various toxic substances introduced from without or produced within the body. The typical urticarial wheals of the former group are produced by the bites or stings of various insects and by various physical, chemical, or traumatic agents. Among the internal or constitutional causes may be mentioned hypersensitiveness to foods, drugs, and sera; infections; intoxications; metabolic and nervous disturbances. The various etiologic agents are legion, yet many times not any can be ascertained. Balyeat[1] finds a specific sensitivity to foods in 66.6 per cent of cases, and in 33.3 per cent of cases absorption of toxins from foci of infection or from the intestinal tract.

Walker[2] has reported 3 asthmatic patients who were found to be positive to vegetable proteins by cutaneous skin tests and who developed urticaria when treatment was instituted with the pollen extracts for the primary affliction, bronchial asthma. He also reported 2 patients who developed angioneurotic edema (giant urticaria) when receiving pollen extract injections; one had hay fever and the other asthma. These 5 patients on routine cutaneous tests were found to have the following positive tests; viz., a man of forty-four was sensitive to ragweed and goldenrod, a boy of twelve to ragweed and horse dander, a woman of forty-six to both early and late pollens, timothy and ragweed, a man of twenty-eight to timothy, and a woman of twenty-eight to ragweed.

Grafton Tyler Brown reports one case of urticaria and dermatitis due to grass pollen which did not recur after sixteen injections of grass pollen extract were given in rapidly increasing doses.

The urticarias may be divided into two distinct groups: Group I consists of those urticarias that are associated with mucous membrane lesions such as asthma and hay fever. Reagin can be demonstrated in the blood by the Prausnitz-Küstner method and also by the Walzer technic of passive transfer and feeding the offending food, or by rectal administration, and thus producing the wheal.

Group II consists of those urticarias without mucous membrane lesions. Passive transfer cannot be demonstrated in this group, and the urticarias are usually due to drugs, intoxications or serum, and practi-

*From the Department of Allergy and Dermatology of Northwestern University Medical School.
Read before the Chicago Society of Allergy, January 19, 1931.

cally never to foods. The case we wish to report is of the latter type and no mucous membrane lesion, such as asthma and hay fever, is present.

CASE REPORT

A young woman of twenty-one consulted one of us (C. W.) because of "hives" on her lower extremities, which had recurred every summer for four years. Occasionally, the eruption appeared on the fore-

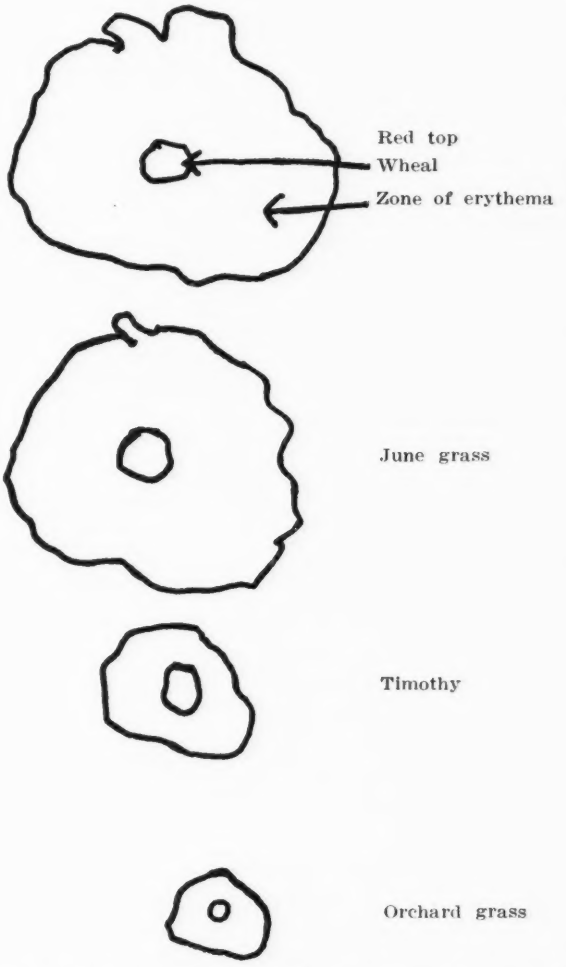

Fig. 1.—Actual size of skin test reactions. Both giant and short ragweed were negative.

arms but usually it was confined to the legs. The eruption appeared quite consistently around June 15 and lasted until cool weather. No therapy had afforded her any relief. Numerous dietary measures and local applications had been tried. The itching was very marked at times, usually more so at the beginning of the attacks, which occurred

at irregular intervals. Her past and familial history were of no significance. Physical examination of the patient revealed only a typical urticaria involving both legs from the knees to the feet to where the slippers covered. The usual laboratory tests were negative.

Because of the desire to investigate every possible angle, cutaneous skin tests were performed. The following groups were investigated; viz., foods, such as meats, eggs, milk, cheese, vegetables, condiments, fish, nuts, fruits; pollens, and a large miscellaneous group, such as orris root, pyrethrum, yeast, and so forth. All of the positive tests were in the Graminae group of pollens; June grass and red top gave strongly positive and orchard grass and timothy gave moderately positive reactions. After these findings it was ascertained that every attack of "hives" followed visits to a tennis court, or golf club. Avoidance of these places has naturally prevented attacks. It is planned to desensitize the patient, if possible. Conjunctival and intranasal tests with grass pollen were negative.

SUMMARY AND CONCLUSIONS

We have described a case of urticaria caused by spring grass pollen.

Avoidance of exposure controlled the attacks.

Very little is mentioned in the literature about urticarias due to pollen without mucous membrane lesions, the case by G. T. Brown being the only one we were able to find and his patient had urticaria and dermatitis.

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Society Proceedings

THE SOCIETY FOR THE STUDY OF ASTHMA AND ALLIED CONDITIONS

The fall meeting was held at the Hotel New Yorker, New York City, on December 6, 1930.

Program

1. **Relationship of Chronic Sinus and Pulmonary Infections to Bronchial Asthma.*** Joseph Harkavy, M.D., and Fred Maisel, M.D., New York, N. Y. (The following is an abstract of this paper.)

IN THE study of the asthma problem in adults, the allergic enthusiast may be confronted with an impasse in at least 47 per cent of cases according to our findings if he attributes the attacks essentially to the phenomenon of protein hypersensitiveness.

Increasing clinical experience in the study of the adult asthmatic leads us to the conclusion that investigation for atopy is only one means of differentiating that from other commonly encountered forms. The authors agree with Alexander that bronchial asthma should be regarded as something more than an effect resulting from a single process, and a broader conception of the disease is bound to lead to more successful therapeutic measures. This broader view lies in the conception that there exists in asthmatics a constitutional imbalance of the vegetative nervous system referable especially to the respiratory tract in which an allergic factor may coexist and be one of the many exciting agents of the paroxysm. When the allergic excitant is absent, other stimuli, particularly infections of the respiratory tract as held by older clinicians, may be responsible and play the dominant rôle in initiating the attacks. That this is so is evident in the fact that similar infections in normal individuals do not evoke asthmatic paroxysms, just as atopens in atopic individuals whose autonomic imbalance is not referable to the respiratory tract, may elicit skin or gastrointestinal symptoms rather than asthma. In other words the shock tissue in the sense of Coca which implies not only a specific cellular but also neural and humoral reaction, varies, dependent on the constitutional make-up of the individual.

*From the Out-Patient Department of Mount Sinai Hospital in New York City.

Such observations lead one to the conclusion that more than one exciting agent can set into action a constitutionally labile vegetative nervous system, and naturally, all the more so, local infections of the respiratory tract which may directly or indirectly, by their toxins irritate the rich network of autonomic and sympathetic nerves supplying the nasal and pulmonary passages, thus precipitating an asthmatic state.

In studying a group of 409 cases of bronchial asthma in adults 200 were found to be nonsensitive. Of this number 132 were completely investigated from the point of view of the presence of allergy as determined by skin tests and infection as established by clinical and x-ray studies of the nose, sinuses, and chest. The underlying causes revealed by these investigations pointed to the fact that the asthma in 87 was primarily due to sinus disease, the ethmoids and the antra being chiefly implicated, while the lungs clinically showed secondary bronchitis with no distinctive x-ray finding. Twenty-two cases had unresolved pneumonia, 4 were complicated by bronchiectasis, and 21 cases had sinus disease associated with unresolved pneumonia. In following up these cases we have noted that when they become free from attacks especially during the summer months the pneumonic infiltration disappears and the lungs heal with the production of adhesions along the diaphragm. Clinically, such cases presenting a picture of asthmatic bronchitis whose x-ray photographs show nothing but adhesions at the base should be regarded as having had a previous or receding inflammatory involvement of the lungs. They undoubtedly harbor a low-grade infection in the interstitium of the lung, invisible with the roentgen ray and responsible for the cough, thick and tenacious mucopurulent expectoration. I feel that the persistence of the interstitial pulmonary inflammation as seen in a more exaggerated manner in the more fulminating cases at autopsy, unquestionably plays a rôle in the difficulties which we encounter in clearing up these conditions.

The chronic bronchitis clinically readily diagnosed only serves as a cloak for the deeper and more extensive lesions within the lung parenchyma. How much latent sinus involvement is responsible for keeping up the pulmonary process even though x-ray examination of these cavities is negative is evident from the comparative findings in two series of cases. In an early group of 57 nonsensitive asthmatics observed between the years of 1923 and 1927, only 7 showed a combined sinus and pulmonary infection. And in a later series of 45 cases, 14 showed such combined infection.

The latter was studied during 1928 and 1929 when increased experience in these conditions caused us to investigate the sinuses more thoroughly. Of this series, a group of 19 had been under observation from three to four years. Of these the youngest was 17 years of age, and

the oldest 60. The duration of the disease was from 1 week to 20 years. Many of these patients had no knowledge of the fact that they had pulmonary infections and attributed the onset of their attacks to an ordinary cold or grippe. The insidious involvement of the lung parenchyma was masked by the more striking bronchitis found on physical examination.

A consideration of these cases points to the fact that the pathogenesis of the asthma was infection of the upper and lower respiratory tract. The attacks followed so-called colds which in all probability were the outward manifestations of exacerbations of chronic sinus infection or the results of recurrent bronchopneumonias. These pneumonias were never completely resolved because of constant reinfection from chronically diseased sinuses.

COURSE AND TREATMENT

The treatment has been largely that of antral washings and topical applications to the ethmoids. Compared with incomplete and questionable nasal surgery these patients have done as well if not better. Infections in individuals whose respiratory mucous membranes offer sites of predilection by virtue of their peculiar constitutional make-up, and whose labile vegetative nervous system is readily shocked in its most vulnerable spot, the respiratory tract, are responsible for the asthmatic paroxysm. Whether the *modus operandi* is an irritation of the vagus and sympathetic nerves by bacterial proteins, their toxins, or histamine substances resulting from the splitting up of the proteins of the host, it is impossible to state at this stage of our knowledge. Coca's definition of hypersensitiveness to infection is conservative, but it should take into consideration the patient, who must be constitutionally receptive.

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2. **Hypersensitiveness to Non-Antigens; a Review of the Literature.** A. F. Coca,* M.D. Discussion by Dr. Carl Landsteiner.†

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3. **Artificial Sensitization of Infants to Poison Ivy.** Henry Straus, M.D., Brooklyn, N. Y. (For complete paper see p. 137, this issue.)

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*To be published in a book on "Asthma and Hay Fever" by A. F. Coca, M. Walzer, and A. A. Thommen. In press. C. C. Thomas, Publisher.

†Dr. Philip Levine to take the place of Dr. Landsteiner, who is called to Europe to receive the Nobel prize.

Item

CHICAGO SOCIETY OF ALLERGY

The monthly meeting of the Chicago Society of Allergy was held February 10, 1931.

Program

1. **Hyperesthetic Rhinitis and Asthma Due to Digestive Ferments.** WM. L. BEECHER.
2. **Résumé of Passive Transfer in Allergy.** L. E. MARKIN.
3. **Review of Recent Books on Allergy, with Comments.** LEON UNGER.

The March meeting was held March 16.

Program

1. **Arthus Phenomenon.**
2. **Tuberculin in Relation to Allergy.** MEYER R. LICHENSTEIN.

Department of Reviews and Abstracts

Selected Abstracts

Histamine Shock and Anaphylactoid Shock. Lumiére, A., and Malespine, A.: Compt. rend. Soc. de biol. **104:** 1010, 1930.

The similarities and dissimilarities between histamine shock and anaphylactic shock are listed. The present work is concerned with experiments to see whether or not protection against histamine shock can be obtained by an anaphylactic or anaphylactoid shock and vice versa. It is well known that protection against anaphylactic shock can be gained by a previous slight shock obtained by injection of a small amount of the antigen to which the organism has been sensitized. If the phenomenon of protection by previous shock holds good for histamine crises, then it might seem possible that an analogy must exist between the mechanisms of these two types of shock.

A male guinea pig weighing 635 grams was injected in the left heart with 0.00005 gr. of chlorhydrate of histamine. A subacute crisis resulted with convulsions and emission of urine. The animal apparently recovered completely within a quarter of an hour and was then injected in the same manner with 0.5 c.c. of an emulsion of sulphate of baryte, a dose always considered lethal. The guinea pig presented symptoms of acute shock but subsequently recovered. The protection in this case was relative.

In a male guinea pig weighing 425 grams 0.0001 gr. of histamine was injected into the right heart. Acute shock resulted, followed by recovery within forty minutes. An injection was then made into the left heart of a suspension of baryte in lethal dose. The animal presented no symptoms of shock, the protection afforded being absolute.

In another series of experiments, the inverse order of injections was used. A guinea pig weighing 595 grams received in the left heart a sublethal dose of baryte suspension. A subacute shock followed from which the animal recovered. Then the ordinarily shocking dose of histamine was injected with no adverse reaction. When, however, the primary injection of sulphate of baryte was made into the right heart, only partial protection was obtained against histamine shock.

From these results, it is stated, the conclusion is drawn that the phenomena of reciprocal protection of one shock by another shock, such as anaphylaxis, extended equally to histamine accidents, suggesting thereby an analogy in the mechanism of the two types of shock.

Potassium and Calcium in Anaphylaxis. Kuschmarjew, M. A.: Ztschrft. f. Immunitätsforsch. u. exper. Therap. **9**: 67, 1930.

A series of experiments upon guinea pigs was undertaken in an effort to make clearer the part played in anaphylaxis by calcium and potassium. The first experiment was in the nature of a check upon the findings of Schittenhelm and Erhard on the presence of potassium in the blood before and after anaphylactic shock. These workers noted a very sharp increase in potassium after shock. In the experiment described in this paper Kuschmarjew shows that while there is an undoubted appreciable increase in the potassium content, there is no such marked increase as that claimed by Schittenhelm and Erhard. In the present experiment the potassium content was measured by the Kramer-Tisdall method.

The second experiment showed that after anaphylactic shock in guinea pigs, the calcium content in the blood was decreased.

In the third series of experiments, guinea pigs sensitized to donkey serum were injected (after the incubation period for sensitization) with a mixture of donkey serum and calcium chloride (0.02-0.059 CaCl to 1000 gm. body weight) controls were used.

Anaphylactic shock was prevented in those animals which had been injected with the calcium. The controls in which no calcium was used reacted with anaphylactic shock.

In the fourth series of experiments sensitized guinea pigs (after the incubation period) were injected with suitable doses of potassium chloride or potassium iodide and treated guinea pig serum. Symptoms of anaphylaxis appeared.

Thus it was shown that an autogenous anaphylaxis could be produced by means of shifting of the potassium balance. It is concluded that anaphylaxis stands in an unquestionable relationship to the potassium and calcium-ion concentration in the vegetative nervous system.

The Relation of Experimental Rheumatoid Inflammation to Allergy. Clawson, B. J.: Ann. Int. Med. **4**: 433, 1930.

It has been demonstrated that by injecting streptococci into the myocardium and the subcutaneous tissues of rabbits, lesions can be produced which morphologically are very similar to the nodules found in the myocardium and subcutaneous tissues in patients with acute rheumatic fever. Experiments were carried out to determine what part, if any, allergy or immunity played in the pathogenesis of these experimental lesions. Streptococci (rheumatic strain) were injected in many places into the subcutaneous tissues of rabbits. A 1-100 suspension of organisms in saline solution was injected subcutaneously into each of 10 places in the backs of all animals on the right side and a 1-1000 sus-

pension was similarly injected on the left side. Five days later the animals were killed and the subcutaneous nodules, if present, were studied by gross and microscopic examination. In these experiments three groups were used:

a. Normal animals.

b. Animals which had been injected intravenously with streptococci (immune).

c. Animals which had been injected subcutaneously in one area with agar at 45° C., heavily seeded with streptococci.

In group *a* the inflammatory reaction was slight, nodules being present in a small proportion. Agglutinins were not demonstrable in any of these animals at the time of the multiple injections. Five days later five of the ten animals exhibited agglutinins in low dilutions. In this normal group (group *a*) an apparent relation existed between the presence of agglutinins and the number, size or character of the nodules.

In group *b* the animals had been immunized by an intravenous injection of streptococci. Multiple injections were then made subcutaneously at intervals of 1, 2, 3, 4, 5, 6, 7, 8, 10 and 12 days. The group was subdivided into:

1. Twelve animals receiving the multiple subcutaneous injections in from 1 to 5 days after the original intravenous immunizing injection.

2. Eleven animals receiving the multiple subcutaneous injections in from 6 to 12 days after the original intravenous immunizing injection.

In group 1 the inflammatory reaction was slight.

In group 2 the inflammatory reaction was marked.

Two factors were considered as possible explanations of the quantitative difference in reactions in these subdivisions of group *b*. The factors were: (a) The time of multiple subcutaneous injections after the original immunizing injection. (b) The degree of concentration of the immune bodies in the blood of the animals.

Allergic reactions are likely to take place in from 6 to 15 days after initial injection. The allergic factor then is absent in subdivision group 1 but present in group 2.

In subdivision 1 the concentration of antibodies in the blood was low, never exceeding 1:200 at the time of the multiple subcutaneous injections.

In subdivision 2 the concentration was high, reaching 1:6400.

An attempt was made to determine whether hypersensitiveness or the high antibody content in the serum was responsible for the marked inflammatory reaction, greater frequency and larger nodules of subdivision 2. Eight rabbits were highly immunized by four intravenous injections at intervals of 5 days. Multiple subcutaneous injections were then given. The agglutinating titer was high—1:256,000 and 1:300,000. Few nodules developed and it was concluded that increased antibody content played an appreciable part in the reaction originally

shown in subdivision 2 of group *b*. This should be attributed, rather, to an allergic reaction.

In group *c* hypersensitive rabbits were injected in one place, subcutaneously with 5 c.c. of melted agar at 45° C. heavily seeded with streptococci at the point of inoculation. An abscess regularly developed. From 12 to 15 days later, multiple subcutaneous injections were made as in groups *a* and *b*. The reaction was pronounced. The greater degree of reaction was not due to a high antibody content, for the agglutinating titer never rose above 1:400 in any animal in this group. The authors state that "something bound up with the abscess seemed to be responsible for the hypersensitiveness."

In all 3 groups two types of cellular reaction were noted:

1. The exudative. 2. The polyblastic.

No difference could be found in the character of the polyblastic reaction in the nodules of the normal, immune or hypersensitive animals. However, doses which in normal or immune animals have no apparent effect, in hypersensitive animals will stimulate the production of definite nodules and abscesses.

In conclusion, it is stated that the "relationship between allergy and the polyblastic type of reaction as seen in human rheumatic and experimental lesions, appears to be not a qualitative but a quantitative one."

Bacterial Hypersensitivity of the Intestinal Tract. Dorst, S. E., and Morris, R. S.: Am. J. M. Sc. **180**: 650, 1930.

An investigation was undertaken into the possible relationship between a well-recognized group of clinical symptoms (often variously and incorrectly diagnosed as chronic appendicitis, peptic ulcer, chronic cholecystitis or spastic colitis) and bacterial hypersensitization of the enteric tract. Attempts to find some unusual flora in the entire tract to which the patient might be sensitive, proved unsatisfactory. Skin tests with extracts of such flora gave negative or undecisive reactions. Very different results were obtained with extracts of the so-called "normal flora." Extracts of *B. coli communior*, *B. coli communis*, *B. acidi lactici*, *B. fecalis alkaligines*, and others were made and skin tests carried out upon a group of 30 patients, all of whom had symptoms of long standing. Twenty-six of the thirty patients showed marked sensitivity to one or more of these strains, the most common being *B. coli communior*. To test the statement that has been made, that all individuals will show marked symptoms when *B. coli* strains are injected, all the patients in a medical ward who were not seriously ill, were tested. Of these patients over 50 per cent failed to give positive reactions, and of the remaining number almost all who reacted gave a history of gastroenteric disturbance.

Desensitization was attempted of those patients sensitive to "active" strains. The desensitization was carried out in the usual manner, with small doses at daily intervals. In a group of over seventy cases, symptoms completely disappeared in over thirty and there was a marked improvement in the majority of the remainder.

Previous experiments suggested the possibility that sodium ricinoleate might exert a detoxifying action on the organisms capable of producing positive skin reactions in patients. Heat-killed suspensions of the various strains were subjected for twelve hours to a concentration of 1 per cent sodium ricinoleate. The organisms were then packed and washed free of the sodium ricinoleate. Patients already known to be sensitized to the normal enteric flora were then injected simultaneously with treated and untreated strains. The untreated suspensions provoked violent reactions but the treated suspensions gave rise to no local, focal or general reaction. A patient who could tolerate only a very small dose of untreated suspension could tolerate many times that dose when the treated suspension was used. In treatment, the detoxified vaccine was substituted for the untreated vaccine with no impairment of the antigenic properties. The best results in treatment were obtained by the combined use of detoxified vaccine and sodium ricinoleate administered orally (5 grains of sodium ricinoleate suspended in olive oil and enclosed in a soft enteric capsule, which eliminates the irritation otherwise encountered in the oral administration of sodium ricinoleate).

The authors conclude that there is shown to be a definite relationship between enteric disturbances and a bacterial hypersensitization of the enteric tract.

The Pathogenesis and Therapy of Old-Age Asthma. Müller-Deham, A.: Wien. klin. Wchnschr. **43**: 1273, 1930.

One of the most frequent complaints of old age is shortness of breath. It is a recognized fact that with age, with frequent emphysema and chronic bronchitis, attacks of an asthma-like dyspnea appear. Clinically, this so-called old-age asthma presents a picture very similar to that of true bronchial asthma: expiratory dyspnea and stridor, straining of the auxiliary muscles, inflation of the thorax, expectoration, attacks at night and especially in the early morning hours, etc. Eosinophiles in the blood and sputum—the usual finding in the cases of early asthma—were, however, seldom found in the author's experience of old-age asthma. The therapy was similar to that used in bronchial asthma. Adrenalin was found to have an excellent effect and no contraindication was found for its use. The same was true for ephedrin. Other therapeutic measures, such as sprays and the smoking of asthma cigarettes the author does not discuss in detail, stating merely

that, as in bronchial asthma, they are unreliable and individually very variable, but are of some use. Concerning the use of two drugs—atropin and iodine, there is a detailed discussion. The use of atropin is discouraged because its protective power is not very great and because its effect upon vision and appetite is not good. Treatment with sodium iodide gave excellent results.

With a strong analogy between bronchial asthma and old-age asthma in the clinical picture and in therapy, it was thought that a future similarity might be found in the pathogenesis. Experiments were undertaken to discover the possibility of a skin reaction to some allergic condition. Thirteen cases of old-age asthma were tested cutaneously or intracutaneously with extracts of animal danders, foods, bacterial allergens from sputum, mould extracts and in some cases, pollen extracts. The extracts were made according to the method of Storm van Leeuwen. Controls were used. Results showed in the thirteen cases of old-age asthma positive reactions without exception to sputum bacteria and mould extracts. A high percentage of nonasthmatic controls (25 patients of ages between 50 and 87 years) also gave positive reactions. To the other extracts there were only occasional weak positives among the thirteen subjects and none among the controls.

The thirteen patients were treated with twenty injections in increasing doses of the bacterial and mould allergens to which they had given positive reactions. The results, for the greater part, were very satisfactory. The attacks became more infrequent and the dyspnea lessened. In individual cases the improvement was very marked. It is stated in conclusion, that the specific character of this therapy is questionable.

Bronchial Asthma Caused by Liver and Liver Extract Diet in a Patient Suffering from Primary Anemia. Matzger, E.: J. A. M. A. **96**: 110, 1931.

A case report is given of a patient in whom the diagnosis of primary anemia was established. The patient also suffered from bronchial asthma, the attacks occurring about once a month. There was no family history of allergic disease. The patient was put on a diet of raw liver. After two weeks the anemia responded but after one week of the diet the bronchial asthma became constant and continued so until the discontinuation of the liver diet. Desiccated hog stomach maintained the desired blood picture without causing asthma, however. The patient again took liver extract and there was a return of the asthmatic symptoms. These symptoms disappeared on the discontinuation of the liver diet.

Skin tests were made revealing the patient sensitive to a variety of substances. Upon active immunization with house dust and rye the patient became free from asthma and hay fever.

It is not considered that liver and liver extract can be the causes of asthma but it is suggested that they may cause other allergic manifestations, and therefore they may be asthmogenic.

On the Question of the Identity of Animal Hair Allergy (Horse, Cat and Dog Hair Allergen). Storm van Leeuwen, W.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **68**: 427, 1930.

It was observed that patients who gave a positive reaction to one animal hair allergen usually gave a positive reaction to other animal hair allergens. This observation led to experiments to discover whether or not the animal hair allergens were identical or at least contained a common factor. Extracts were made of horse, cat and dog dander. These extracts were used to test 36 animal hair sensitive patients.

Results showed:

Positive to horse	30 patients
Positive to cat	29 patients
Positive to dog	22 patients
Positive to horse, cat and dog	18 patients
Positive to horse and cat Negative to dog	24 patients
Positive to horse Negative to cat	6 patients
Positive to cat Negative to horse	5 patients
Positive to dog Negative to horse and cat	1 patient

These results showed that the primary skin reaction which was elicited in hypersensitive patients through the allergens of horse, cat and dog dander, was not dependent upon a common factor in these allergens, and there is no identity among them.

It was further observed that a desensitization of a certain area of the skin through repeated injections of a given animal hair allergen often gave rise to a desensitization of the area to other animal hair allergens. Experiments with animal hair allergen were carried out to discover whether this desensitization might be attributed to a common factor in these allergens. In 18 cases of animal hair allergy, desensitization to a given animal allergen was accomplished on 31 separate areas of skin. After the reaction became negative sensitivity to one of the other two allergens chosen, was tested.

Results showed that after an area of skin had been desensitized with an animal hair allergen which elicited a strong positive reaction from the patient, the reaction to other animal hair allergens was greatly diminished or disappeared. In those cases, however, where the original allergen used for desensitization had called forth only a weak response in the patient, the reaction to the other animal hair allergens was only weakened and rarely, if ever, disappeared.

This fact was considered sufficient evidence against the theory that the accompanying desensitization might be due to any common factor among the allergens. It appears, rather that the skin becomes exhausted through repeated allergen reactions. This exhaustion is not due to a depreciation in the reactive capacity of the capillaries for poisons such as histamin and morphine. These have their normal effect.

Passive Local Sensitization in Atopic Individuals. Walzer, M., and Bowman, K.: Proc. Soc. Exper. Biol. & Med. **28**: 425, 1931.

Experiments were undertaken to test the comparative capacity of the atopic and the normal individual to accept passive local sensitization. Atopic and normal subjects were sensitized with atopic serum in a range of dilutions determined by previous titration on normal skins. Seven days after this sensitization, the sites were tested with a dilution of the atopen for which the serum used in the experiments contained reagins. Controls were used. Several atopic sera were used, such as rabbit serum, Ascaris Lumbricoides and timothy pollen. Results showed that the nature of the sensitizing serum was a factor in passive local sensitization in that some patients who failed to accept the transfer with one serum did accept it with another. But regardless of the nature of the serum used, results showed definitely that atopic individuals did not accept local passive sensitization with the same regularity, or to the same degree, as normal individuals. In conclusion, it was stated that this fact must be considered in the interpretation of the results of the absorption phenomenon in atopic subjects.

The Mechanism of Desensitization of the Allergic Skin. Storm van Leeuwen, W.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **69**: 1, 1930.

Reference is made to a previous article in which it was shown that under certain conditions, local desensitization of a skin area with one animal hair extract usually brings about a loss or at least a diminution of sensitivity to other animal hair extracts. The possibility then suggested itself, that the same might hold true for other groups of allergens. Experiments were carried out upon seventeen persons. Seventy skin areas were desensitized and then injected with another antigen,

to which the patients were originally sensitive. Results showed that the desensitization usually held good for the second antigen as well, except in those cases where the original sensitivity to the second antigen was equal to or greater than the reaction to the first one. The theory is advanced that this accompanying nonspecific desensitization is due to the action of an intermediary substance.

Attempts were then made to find whether this intermediary substance showed itself in other ways. A patient was sensitized to an antigen by the Prausnitz-Küstner method of passive transfer and the sensitized area was desensitized by repeated injections of the antigen. In the same place on the skin, the transfer serum was again injected, then again desensitized and the process repeated again. Results showed in the end a negative reaction to the allergen. It was found, further, that the whole skin became exhausted in repeated passive transfers.

These and other experiments in passive transfer were interpreted in the light of an action of the previously mentioned intermediary substance. There is discussion at considerable length of the possible identity of this with Lewis' "H" substance. It is maintained that the localization, at least, of this substance is more peripheral than Lewis thinks it is.

The First Manifestation of the Developing Hypersensitiveness. Dienes, L.: Proc. Soc. Exper. Biol. & Med. **28**: 75, 1930.

In the course of previous experiments the possibility was suggested that in the immunization process the appearance of antibodies in the serum and the development of the usual type of hypersensitiveness might be preceded by a stage in many respects similar to the tuberculin type of hypersensitiveness. This possibility is interesting in connection with the development of immunity in infectious diseases. The followng experiment was performed: Two groups of guinea pigs (4 pigs in each group) were injected intraperitoneally with 0.4 mg. and 2 mg. of egg white respectively. On the 5th, 6th, 7th and 8th day after treatment, the skin test produced with 0.2 mg. egg white was excised from one guinea pig in each group, 6 and 24 hours after the test injection. Skin tests from 3 normal guinea pigs were examined as controls. The controls gave no reaction. The test guinea pigs showed a slight reaction in the microscopic structure, similar to the tuberculin reaction, i.e., a more or less intense infiltration with mononuclear cells.

Histological Study of Skin Reactions in Anaphylactic and Tuberculin Type of Hypersensitiveness. Dienes, L.: Proc. Soc. Exper. Biol. & Med. **28**: 72, 1930.

Experiments were carried out to discover whether in hypersensitive animals there are any morphologic differences between the local reac-

tion due to anaphylaxis and to tuberculin sensitiveness. More than 40 guinea pigs were used and about 180 skin reactions were examined. Reactions were examined 1, 2, 6, 24 and 48 hours after injection and different antigens were used—egg white, crystalline egg albumen, tubercle bacilli, tuberculin preparation, etc. For the study of the anaphylactic type of skin sensitiveness, guinea pigs actively and passively sensitized, normal and tuberculous, were used. Distinct differences in the two types of reaction were noticed. The anaphylactic type of reaction was characterized aside from the circulatory symptoms—by accumulation of polymorphonuclear leucocytes. Mononuclear cells were observed only later and in slight amounts. In the tuberculin type of reaction, on the contrary, the predominant symptom was a strong infiltration with mononuclear cells. Tuberculous guinea pigs, it was noted, sometimes reacted to nonspecific local injections by accumulation of mononuclear cells. The characteristic difference between anaphylactic and tuberculin type of reaction was thus observed only in cases of very slight reactions of anaphylactic type in which the cellular reaction was very slight, both in tuberculous and normal guinea pigs. It is concluded that the differences between the two types of reactions are not only quantitative but are indicative of differences in the intimate mechanism by which the symptoms of the reaction are produced.

Histamin. Küpper, A.: Klin. Wchnschr. **9**: 136, 1930.

It is suggested that under certain conditions, the reabsorption of histamin in the intestines gives rise to disease. The relationship between dyspeptic conditions and increased histamin absorption is considered at some length with special emphasis upon the effect of histamin upon the gastric juice secretion. The author considers to be of great theoretical interest, the relationship between histamin and anaphylaxis. The characteristic syndrome of anaphylactic shock parallels the effect of histamin in many particulars. For example, in the guinea pig anaphylactic shock is characterized by a contraction of the smooth muscle of the bronchioles; the guinea pig reacts with a bronchospasm to the injection of histamin. Parallel effects may be obtained also in the dog and the cat. There is, moreover, a parallel between the sensitivity of different species of animal to histamin, on the one hand, and the intensity with which the animal reacts in anaphylactic experiments, on the other hand. For instance, because of the constancy and high degree of its reactivity, the guinea pig is considered the best animal for anaphylactic experiment; the guinea pig shows the highest sensitivity to histamin of a research animal. The rat, which has a high resistance to histamin, is resistant to anaphylactic shock, either actively or passively induced. It might be considered, according to the author, that anaphylactic shock is nothing other than histamin poisoning.

A relationship between histamin and several allergic phenomena may also be postulated. For instance, in urticaria the dermatographic wheal and the wheal experimentally induced by histamin injection may be shown to be identical. The similarity between bronchial asthma and the bronchoconstriction produced in experimental animals by histamin is apparent. Also, according to Ramirez and George, asthmatics show a stronger local reaction of the skin to histamin injection than do normal individuals.

Correspondence

Indianapolis, Ind.

Editor, JOURNAL OF ALLERGY,
St. Louis, Mo.

Dear Sir:

In going over the issue of THE JOURNAL OF ALLERGY for March, 1930, my attention is again called to a botanical error in the article by Major S. W. French, on pollens of south central Texas. On page 287 under a list of major offenders appears "the ragweeds, both giant and dwarf." On page 289 under *The Ragweeds*, appears the statement "both the giant and dwarf ragweed are present in this vicinity."

My own personal investigation in and around San Antonio several years ago failed to disclose a single specimen of short (dwarf) ragweed *(Ambrosia elatior)*. The plant which is mistaken for short ragweed in San Antonio is slender false ragweed *(Franseria tenuifolia)*.

Since most allergy workers have adopted the term "short ragweed," it seems we should hold to this for a common name for *Ambrosia elatior*.

Yours very truly,

O. C. DURHAM,
Chief Botanist, Swan-Myers Company.